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HUMAN SUBJECTS SUBCOMMITTEE

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ALSO PRESENT:

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Executive Director

MS. HENRIETTA HYATT-KNORR
Deputy Executive Director

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MR. JONATHAN MORENO
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I N D E X

P R O C E E D I N G S

WELCOME

CHAIR CHILDRESS: Welcome to the subcommittee meeting, the Subcommittee on Human Subjects Research. We had a very productive day yesterday, with a lot of important questions arising about the fine draft report that we've been working with and an indication of a number of areas that we need to do further reflection, in particular clarifying some of the concerns surrounding the category of more than minimal risk, non-potentially beneficial research, where much of our discussion focused.

You've seen the agenda for today. The first activity will be looking at the draft report and we will start with the discussion we had yesterday, looking at the recommendations and seeing where we want to go with those.

Then at 8:50 we'll spend some time with Gary Ellis, looking at the discussion of minimal risk, the different understandings of minimal risk, since obviously how we understand minimal risks will -- what these recommendations actually mean. That will come in during the course of our discussion of the draft

report.

Then at the very end of our discussion of the draft report we will talk about next steps, things we need to do to bring this in to something closer to a final version.

Also, as part of next steps we need to think about whether we want to meet in L.A. Apparently the Genetics Subcommittee is going to meet in L.A. I don't have strong feelings about whether we meet or not. We may just want to see where we stand at that point and then make a decision about whether to meet.

Then we'll have a discussion with Jack Schwartz, who has appeared before us a couple of times before, on the Maryland Attorney General's Working Group involving draft recommendations from that group on decisionally impaired research subjects. And Bill Freeman will give us an update on the survey of Federal agencies.

We'll talk after statements by the public. Let me just mention that it would be helpful if members of the public would indicate if they would like to testify at that point so we'll have some idea of how much time will be required. So you can just sign up at

the back and indicate to a member of the staff that you would like to testify at that point.

Then we'll discuss future Commission research activities and building on the report of Eric Cassell's committee, and then draw some conclusions.

Adjournment would be no later than 12:30. I guess I'll probably be surprised if we run until 12:30, although we obviously have a lot of important work to do, particularly on research with decisionally impaired subjects.

Any other points to get out before we get down to work? Harriet, do you have any?

MS. HYATT-KNORR: Not right now, no.

CHAIR CHILDRESS: Okay.

MR. CAPRON: Two questions. The first, is whether we need to have some discussion this morning on the question of the Federal office issue that we heard about yesterday, and that the Commission as a whole had a discussion on. We do not have -- document yet.

CHAIR CHILDRESS: Right. She hopes to have that by the end of the month, if I recall correctly.

MR. CAPRON: Maybe it's premature, but I did have a slight sense that we were all frustrated that we

got the issues out. There seems to remain a great deal of consensus, but we need to make the determination of which is the level we want to recommend.

CHAIR CHILDRESS: Well, let me raise the question this way, Alex. I think many of us, I suppose, are in a transition period of moving more toward whole Commission work, away from subcommittee work.

I think one of the frustrating things about the previous meeting was that we had such a fine discussion with John Fletcher and Charles McCarthy on this particular topic, a discussion that actually would have been very beneficial to the group as a whole. You did a fine job yesterday of giving the background for that and summarizing it.

So I don't know. It would certainly be possible to spend a few minutes talking about some quick responses, but it seems to me that would be a discussion that would be very useful for the Commission as a whole to have.

MR. CAPRON: I agree with that. I'd like to know how we're going to have a document that will bring together the contact review that we had. I mean, it

seems to me that in some way, most logically, this is a chapter of our Federal agency's report.

I mean, it is a much more substantive conclusion to that report than simply reporting on restraints and weaknesses of the responses in different agencies. This is taking that picture and saying the conclusion to be drawn is a little different than simply tinkering.

CHAIR CHILDRESS: Right.

MR. CAPRON: I entirely agree. I wasn't really trying to say that we needed discussion here now, I just wanted to get some sense of how this fits into your time table.

I think as far as the subcommittees, I mean, my hope is that the subcommittees are history and when we talk about meeting on these topics from now on we're talking about all of the --

CHAIR CHILDRESS: Good. No. I quite agree with you. I guess the current plan, and we'll talk about this a little more when Bill Freeman reports, would be to finish the report in the area of genetics on tissue samples and to finish the report on decisionally impaired research subjects, and then to

finish the report on the Federal agency. So that would give some sense of the timing. As I understand it, that's the time frame.

Let me get Eric in and he can really address it better.

DR. DUMAS: Well, I see the subcommittee's working on behalf of the whole, so I wouldn't have any objection at all for this subcommittee to make recommendations, specific recommendation, to the body in regard to this issue which I think we can settle and move it off of the agenda. It seems to me that there is a lot of agreement that we need a place to take care of these concerns.

So, I feel impatient to get the things we can make decisions on decided. My suggestion would be that we discuss the report, that we make a recommendation to the body as a whole, and that we'll move that part of our business forward.

CHAIR CHILDRESS: And I think there is a lot of wisdom in that. The only problem that has come up is that it is often difficult, and we saw this in the discussion yesterday, to recapture the kinds of arguments, and particularly some of the powerful

elements attached to them, in the context of the larger discussion after we've had the subcommittee discussion.

In this particular area I think we've lost a lot in not having the whole Commission hear those two reports last time. I think we'd be a lot further along.

So the question is whether we want to spend the time doing it today or whether, as I think I like the suggestion that we really talk more about a plan for doing it with the larger Commission. Eric?

MR. MESLIN: The only thing that I would add, substantively, is just on the organizational front. It would be very useful for us to have Dr. Gonzales' paper in hand, and we should have that within the next, we hope, week or two.

Although that is not identical to the McCarthy-Fletcher proposals, complementary as they may be to each other, that was part of the process of gathering some findings that will inform the Commission.

I think it will be entirely possible for staff to put together a document that both summarizes where the debate is and, with input from Commissioners,

provides a framework for how to resolve this issue and, as you say, get it off the table.

It is a fairly important subject and I think we'd like to hear a bit more from the Commissioners at the appropriate time--this might not be it, unless you feel the need to speak up--as to whether it will join the Federal agency's survey as an appendix or a chapter or whether it will be a stand-alone document that will accompany it.

So this is something that we can continue to discuss, but it is a high priority subject because, as you say quite rightly, it is something that we can attend to, having heard a good deal of conversation already.

CHAIR CHILDRESS: Rachel, sorry. I hadn't noticed that you were here. Did you have anything you wanted to say at the outset?

MS. LEVINSON: No. Just let this continue.

CHAIR CHILDRESS: Okay. Any further points about this?

MR. CAPRON: Well, not a further point, but I'd like to sort of see where we're going on the conclusion. Could you give us a sense then, would it

be reasonable to expect that at the March meeting we would have from staff, or the April meeting we would have from staff, a document drawing on the previous discussion, drawing on yesterday's discussion -- in a way, what I was, in a very rough fashion, trying to do orally was to present what seemed to me to be the elements that would go into that, abstracting them, boiling them down from the excellent papers.

If the staff has that material -- I'm with Rhetaugh on this, that it doesn't seem as though it should take up a lot more of our time and we ought to move on.

But I think that we're at a point on many topics where moving on means having not the oral agreement, which we seem to have, largely, but really on the table the draft document, and we can sign off on that, even if we saw, well, we're going to hold it for a month or two, or three or four, while it goes into some other document which won't be ready until that time. That's fine. We've gotten through that. I just want to get a sense from you, are we saying March, April?

MR. MESLIN: I see no reason why it couldn't

be available by the March meeting, with two caveats. One, based on your very helpful overview yesterday, I'd hoped you would be able to provide some substantive input into the writing, either by reflecting on some of the documents or offering some proposed solutions for the Commissioners to debate. I think the point of whether or not there is agreement should go not unchallenged.

I think there was certainly agreement that something different ought to occur. There was not agreement as to either the exact location or what the administrative arrangements for putting that office into place would be.

I think there it would be fruitful to have some further discussion by the Commission. But I think you're entirely right, it could be done by March with input, not just from you but from Alta Charo, who is not here, and had an interest in providing some commentary.

MR. CAPRON: Well, Alta, I should say--and I should have made this more clear--and I did discuss this, and I think I was reflecting her views as well. So let's look at the March meeting.

What I would personally urge, and maybe we need a straw vote now and maybe only if that draft is there, you could, as the staff, give us the document then with two concluding sections, one of which says the McCarthy-type version, the other says the Fletcher, then we could have the discussions once we have those before us.

I would hope that you would vet the idea with it as widely as you think it's appropriate so that, beyond the thoughts of Fletcher and McCarthy, there may be further refinements, there may be issues that are essential to be addressed that they haven't addressed, et cetera.

CHAIR CHILDRESS: Yes. Okay.

Rhetaugh, do you feel comfortable with this direction?

DR. DUMAS: Oh, yes. I'm flexible.

CHAIR CHILDRESS: It sounds as though you want it moving forward.

DR. DUMAS: Yes. I just think we take too much time --

CHAIR CHILDRESS: We hear you.

DR. DUMAS: -- to make decisions around here.

But I can't have it my way all the time.

CHAIR CHILDRESS: And I'm assuming that you could provide, for example -- I think it would be very helpful if all of us would have a print-out of your --

MR. CAPRON: Yes. I can do that.

CHAIR CHILDRESS: That would be helpful. Okay.

Anything else we need to talk about regarding our agenda?

(No response)

CHAIR CHILDRESS: Okay. Let's start with the -- well, let's see. One more thing. Let me note that everyone should receive at the table this morning a copy of the 10 or 12 pages provided by Paul Oppenbaum for insertion, with modifications, the two sections of Chapter 1, and we'll come back to those pages in due course today.

Was there anything else we needed to --

(No response)

CHAIR CHILDRESS: All right. Jonathan, anything you'd like to say following yesterday's discussion? We will start with the recommendations, pick up where we left off yesterday, and then move to

other portions of the draft document.

RESEARCH WITH DECISIONALLY IMPAIRED SUBJECTS:

DRAFT REPORT

Discussion: Led by Jonathan Moreno, Ph.D.

DR. MORENO: It seems as though we should start by talking about the status of the Research Advance Directive Concept, either the nomenclature or the substance. It would be very helpful, I think, to start there and resolve that question.

CHAIR CHILDRESS: And I'm going to try to get everybody to use microphones.

MS. FLYNN: It would be helpful to me, and maybe I'm -- little discussion on substance, I'd like to hear a little bit from Rich and others before we go further. I feel that, yes, the discussion was useful, but I don't think we got a chance to complete it and I'd like to share a little bit more substantively.

DR. MORENO: Can I just say one thing about that discussion? I'm not sure that in the discussion a key element of the Research Advance Directive Concept was suitably addressed, namely for people who -- actually, Trish has talked about this with me, and I think is reflected in the text.

For people who are anticipating a period of

incapacity, who've already experienced it, these truly would be advance directives. I'm not sure that that concept was fully appreciated in the discussion yesterday.

So that even if, in other respects, the concept of an advance directive for this kind of research proves not to be importantly different from informed consent, garden-variety informed consent, at least in that kind of situation it would seem to be useful.

CHAIR CHILDRESS: Good point.

Trisha?

PROFESSOR BACKLAR: Yes. That is -- it's terribly hard for me to hear people speak, I must say, even when they're speaking into the mike. And it may be my advanced age, but I urge all of you to speak clearly as possible.

MR. CAPRON: Because this is an airplane hanger and there seems to be some loud noise coming.

PROFESSOR BACKLAR: It gets distorted. Yes. It's really horrible. Now that I've said that, let me put it aside.

Yes. Exactly and precisely as you said,

Jonathan. These are people who have experienced, and may experience again, periods of an inability to do decision making, periods of incapacity. So what the advance concept is planning for those periods where they may not be able to make decisions about their involvement in the research -- so it is not a misnomer, for that particular group, to call it an advance directive.

In that same way, it's no different from an advanced directive for psychiatric treatment, so that there are certain things that will fall into place should that capacity for decision making be lacking.

I don't think I need to spell out the rest of it, because what we tried to build into it were protections inasmuch as there would be a top decision maker, there would be an outside provider who was not connected to the research, and that provider did not need to be a physician, it could be a case worker, et cetera.

CHAIR CHILDRESS: I think it's very important because it clarifies what this is about, but also limits it. I think that the -- limitation group of subjects to whom it would apply is also very important.

PROFESSOR BACKLAR: And because there was this -- it is also important to understand that what was intended in this process of planning was that during the consent process that takes place in any research protocol, one hopes, is the appointment of the -- the proxy should be involved for somebody who is in that situation where they may lose their capacity. So if the proxy doesn't come in later, in other words, people are -- the proxy is educated at the same time and learning about it along with the person, the subject.

DR. MORENO: And it's worth knowing that the current, much maligned chart on page 150, for the category of greater than minimal, non-beneficial research, the current framework calls for having -- whether there's informed consent or an advance directive, calls for having the necessary involvement of a legally authorized representative, as well as the health professional monitor, which would go to Trish's wish to ensure the involvement of such an other person in the process.

PROFESSOR BACKLAR: And there seemed to be some confusion yesterday, and I'm not certain it is in the document, Jonathan, as you've written it--I tried

to find it last night, but I'm afraid my eyes were closing--about whether or not that surrogate could be a family member.

DR. MORENO: Absolutely.

PROFESSOR BACKLAR: I is my intention that it absolutely could be.

DR. MORENO: Yes.

PROFESSOR BACKLAR: It didn't have to be, but it certainly could be.

DR. MORENO: Could be. And I had tried to work Number 4 on page 145 in such a way that would invite the local jurisdictions to develop their legislation for regulations in such a way that there could, indeed, be a default mechanism. That's what people wanted yesterday.

PROFESSOR BACKLAR: I also would like to say one thing that I don't think was clarified yesterday. There was a lot of discussion about people didn't think -- advance directives. I wasn't seeing it as a matter of choice, that if you had a subject who could lose their capacity for decision making, it would be built into the process of consent.

So it wasn't, oh, you won't have -- if you're

not going to have consent to a research protocol, then you might not have an advance -- whatever we're going to call it, you might not have this particular operation.

DR. MORENO: Well, the incentive is -- if you look at the chart. For greater than minimal, non-beneficial research, largely, is the language I'm using to describe that kind of study. You have to either get the informed consent of the subject, which is presumably proximate within a matter of hours or days of initiation.

CHAIR CHILDRESS: A couple or three of us are having problems hearing you. I'm not sure it's the microphone.

DR. MORENO: Let me try again.

MR. MESLIN: And speak a little more slowly, if you would, Jonathan.

DR. MORENO: For greater than minimal, non-beneficial research, I would be -- as the current framework is written, the investigator would have to get either the informed consent of the subject, which is presumably pretty much proximate to the initiation of the study itself, the matter of hours, but at the

most a few days, or an advance directive authorizing this kind of research.

Now, we can argue about what this kind of research means. I'm not sure the research sorts itself into actual kinds a là Aristotle, but, nevertheless, it's a way to get started in this discussion. So the pressure on the investigator is precisely of the kind that Trish has just described for this category of this research.

That would not be the case for potentially beneficial research in which you would get either the informed consent of the subject if the certain situation is right, or we get the advance directive, or permission of the legally authorized representative, which could be, again, the family member.

But when there is a greater than minimal amount of risk and it's not beneficial, this framework would encourage the investigator to get either informed consent or, alternatively, the advance directive.

PROFESSOR BACKLAR: Again, this, of course, brings us back to something we need to talk about and which we are maybe talking about, because I find it very confusing not to know what we are meaning when we

talk about these breakdowns, more, thus, and so on and so forth, because intuitively I want to say that there are a group of people which -- and I think we'll get back to this, that almost anything that you're going to do -- research with a particular group of people, that you may want to have certain protections in place.

CHAIR CHILDRESS: Let me just point out that this draft also, for those of you who have memorized it, as with the previous draft, on page 146 it tries to deal with the minimal risk definition problem by using examples and actually suggests that those examples might even be written into regulation.

PROFESSOR BACKLAR: I couldn't hear you.

CHAIR CHILDRESS: Okay. This draft, as in the previous draft, tries to deal with the question of the definitional problem for risk by using examples that might even be written into regulation.

Now, one could go further and do as the Canadians have done recently and stipulate that there is perhaps a different scale that is appropriate for people who are lacking capacity with respect to what counts as risk. So one could even add that kind of statement to make the point clearer. Thanks to Eric

Meslin, for providing me with that document.

PROFESSOR BACKLAR: But again, I want to say that I'm hoping that the discussions we have with Gary Ellis is going to sprint us forward in being able to make this --

CHAIR CHILDRESS: So we'll come back to the minimal risk part. I have Alex -- just a moment. Laurie, does this help get under way the kind of discussion -- I think it's helped clarify some of the issues and I think one of the critical things you have to decide is basically whether we pay too high a price in terms of research if we have restrictive conditions of this sort, and that was the debate between Zeke and Alex yesterday.

MS. FLYNN: Yes, I think it is helpful and it reinforces my concern that I expressed yesterday, that we are, indeed, I think unwittingly, erecting too great a barrier to research that I think is a modest increase over minimal risk and is, in fact, quite essential at this point in terms of basic neuroscience.

CHAIR CHILDRESS: Trish, did you want to get a response in?

DR. SCOTT-JONES: I just wanted to say that I

don't think that there's -- that when you have vulnerables on any subject, that one must be very concerned about their protection. The costs may be very small in comparison to the kinds of costs that go into research anyway.

MS. FLYNN: My concern, and I certainly agree, was actual limitation and whether, in fact, this current structure would essentially obviate much of the research that is now going on.

CHAIR CHILDRESS: Did you want to address this --

DR. SCOTT-JONES: I wanted to ask Laurie to just say a little bit more about the point that she just made, because I think it's important at this stage because we want to come to some sort of consensus to really hear what each of the commissioners is saying.

Laurie, I was just wondering if you could be more specific. Do you think it means that there would be additional costs, there would be too much time taken up with the consent process, or what specifically would you see as the obstruction to the research process?

MS. FLYNN: I guess I would want to recommend that we hear from some who are directly involved in

administering or conducting research, because I'm not one of those people. But it seems to me that the large number of studies that are now under way that represent a minor increment over minimal risk needs to be analyzed.

I guess my concern has been that we've looked at this in terms of, how do we try to stop certain kinds of research or how do we try to limit certain kinds of research.

My focus has always been on, how do we extend, expand, and improve both the informed consent process itself, which I think we don't have nearly enough attention to here, how do we educate IRBs and engage the community of interest in the work of the IRB so that the design of the studies, including the protections and consent procedure, can be strengthened?

This appears to me to be moving to a kind of narrower approach of, some research is okay and some research is not. I'm not comfortable that we know enough about that research and about the vulnerability of that population in any particular study to make those kinds of final judgments.

CHAIR CHILDRESS: I guess one question would

be, and this came up yesterday, what additional information we would want from whom to help think about this matter. Jonathan, then I'll get Alex's response.

DR. MORENO: I think this is an empirical question. How much research is going on that involves a minor -- right now that could not be done under the conditions described in this proposal? I think that is a very important question. I'm not sure anybody really knows, Jim, with a high degree of reliability the answer to that question, but it's one that we might well want close to the OPRR.

CHAIR CHILDRESS: Alex.

MR. CAPRON: I endorse that view, but I wanted to address something else, if it's all right.

CHAIR CHILDRESS: I'm sorry.

MR. CAPRON: We're sort of having two discussions. You're talking about advance directives, then we're talking about what seemed to me to be a very fundamental point that arose in the meeting yesterday, which is, if we had made the categories too simple we'd collapse too much in. We need to unpack some of that so that we don't protect people out of the opportunity to benefit from new science.

I'm very concerned that we figure out how to go about this, because I don't think it is just a matter in this case of hearing from OPRR. I think it is probably a matter of hearing from, on the one hand, researchers, and on the other, some who have observed the abuses of research.

Among the researchers, also, to find out whether there are colleagues who say, well, it's true, you could do the research that way, but you would also do the research this way with a group that has the ability to provide consent.

To me, the hardest case that Laurie raised was, if there were fundamental scientific questions that would only be answerable in subjects who, throughout their life, had a permanent incapacity to provide consent and where you were automatically putting in a surrogate, and if some of that research fell within our more than minimal risk category, it would never be doable because we see some requirement for the individual to consent.

What I wanted to do, however, was come back to the discussion that Trish was having a moment ago because the one thing that did come out yesterday in

our discussion with the larger Commission, and I feel that in that discussion I was a proponent of, more or less, what we had here about the advance directives.

But I realized that in the discussion we may have been using the terms in different ways. There is the circumstance which is, I think, and correct me if I'm wrong, Trish, the one which you seem to have in mind most of the time when we're talking about this is the person who not only has fluctuating capacity so that they have some experience with their illness and they have periods when they are quite able to participate in their decisions, but for whom it is possible to specify with a good deal of accuracy what the research protocols would likely be that they are being asked to participate in.

And it's just a matter that, we won't do this research on you while you're in the state that you're in when you're able to consent, the time we need the study, whether it's a physiological study or whatever, metabolic study, or a study of a medication, or whatever, is at the point where you have manifestations of your illness that would not make you able to consent.

That seems to me to be captured by avoiding the phrase "advance directive" simply by some notion of prospective consent. That is to say, you are actually going through a consent process the way you would if you were going to have an intervention tomorrow, but the understanding is that this intervention will not occur for weeks or months, or it is even possible never, in your case.

If you never went back down in that part of the cycle of your illness, you would never be a suitable subject. That is just a hypothetical. That is not very problematic, it seems to me. We could address that with some phrase about prospective consent.

Now, when you can join that with durable powers of attorney for health care, which are not just about end-of-life care, you can have a situation in which the person is able, under the law in most states, to also appoint an agent at that time, and one would hope that right from the beginning from that point the agent is involved with the researcher in learning about the research and being really prepared, with the subject, to take on that role of the on-the-spot

decision maker.

The harder cases are the ones which I thought were also encompassed in looking at the materials here on pages 121-125 or so, or 127 or so, I wasn't at all clear whether we now were saying this or not.

I thought we were also thinking about something which really comes closer to me to being an advance directive because of its generality for patients who are sliding toward a state where they won't be able to make decisions, the dementia patients, in particular, but whose course is not so advanced that you can't engage them in discussion, but they're clear enough about the fact that they know that's where things are going and they may have a number of years of life there where the question would be -- at least one question one could ask is, are you willing when you are in that state to be involved in a study which wouldn't be for your immediate benefit, which would have no potential for benefit for you, and would have some increment over just minimal risk of the type that is more or less part of daily life.

For that, some phrase about advance directive is certainly suitable. But I couldn't tell, Trish,

whether you, in the exchange with Zeke, were actually saying, well, no, I'm not thinking about advance directives for that group.

And I obviously don't know what the rest of the commissioners say. It seems to me that there really still is a difference, and my sense was that you had two categories of potential subjects, those who have told you, I'm willing to have this happen, and those who haven't told you this. Now, this is relevant to the pages we have in front of us because--I think it's on page 123--there's some suggestion of -- the top of 123.

For instance, "Research Advance Directives might only be valid when the research presents some prospect of patient benefit and strict time limits could be imposed that require the renewal of a living will."

Then there's a reference to the option of the appointment of the legal representative, which is really the discussion of the next section here, so it's kind of out of place.

I would like us to highlight at some point here, if we're in agreement, that the advance

directives has the ability to play this useful role of separating people who are willing to say now, I will take greater risk for something that won't benefit me, from those who aren't willing to make that commitment.

I disagree with Zeke on the notion that if you took a poll among this category of people and you had 80 percent of them saying it would be all right to do this, but only 20 percent of them will sign a directive, that that's an indication that the directive method doesn't work, the same way it doesn't work when we know that the public says they want a certain kind of end-of-life care and they don't get around to filling out advance directives about their end-of-life care.

One of the things that I believe is valid about the end-of-life care, and I would certainly say is valid about this, is there's a huge difference between expressing a general opinion and committing yourself that this is a course you're willing to follow, and that barrier of not signing the papers isn't just due to laziness.

There are psychological factors that would lead a person to say, if asked generally, well, do you

think that's research that ought to be able to go on, yes, will you sign up for it, well, let me think about it, and then they never sign up for it because they actually have a reluctance. They don't want to be the subject of such research.

So it seems to me that it's a reasonable sorting process between those people who ought to be made unavailable for such research by the fact that they haven't committed themselves to be available.

Now, one final note. All of this is against the context of what used to be the law, and I have not researched this recently, but one of the conundrums for research with children and with those who can't make decisions is, the old view used to be, people in this situation cannot be used for something that doesn't have some prospective benefit for them.

You can't be a surrogate decision maker and allow someone to be used. Now, we've said, well, let's make a small exception to that. If there really is no more than minimal risk, isn't this the kind of thing that most people could be presumed to be willing to run? Sort of a consensus grew up, yes, that's all right after all.

But when we get beyond that more than minimal risk, it seems to me that we are correct in saying that the old view really ought to be adhered to, which is a surrogate, appointed or otherwise, who can't go around consenting people to something that isn't going to benefit them. I mean, it's the archetype of the exploited person.

PROFESSOR BACKLAR: That's right.

MR. CAPRON: Maybe we should have a discussion on that, and I have a couple of other points in here, Jonathan, about what we say along those lines.

CHAIR CHILDRESS: Let me let Trish respond directly, if I could, Eric, from there.

PROFESSOR BACKLAR: I do think that it would be extraordinarily helpful, instead of -- in this more abstract way, and I have -- is to situate a situation in which one would use an advance directive like this, and of course, the infamous now UCLA protocol would be a perfect place for this. I'm not going to repeat what that -- is, because I've done it enough times.

So you could use a little scenario. It would work in this. Then you'd start to move it along to these other scenarios. When I responded to Zeke

yesterday it was because I had thought it through very carefully in terms of some research protocol like UCLA. As we moved along, for instance, into prospective dementias, Alzheimer's, you need to alternate the model somewhat. It doesn't stay rigidly the same.

There has to be some way in which we could describe this not being quite so rigid, at the same time keeping those protections in place. That's why when we discussed about Greg Sachs, who's done quite a lot of work here in this, we could use some of his models. So it isn't just one rigid model.

CHAIR CHILDRESS: Absolutely. But I think it's also the case, at least judging from my conversations with you, that you would have no objection to our getting rid of the term "Research Advance Directive" to cover the whole area.

PROFESSOR BACKLAR: Absolutely.

CHAIR CHILDRESS: I think it is misleading.

PROFESSOR BACKLAR: I'm not married to a term, I'm married to a concept.

CHAIR CHILDRESS: Well, and I think that the term, though, brings in some other things -- association. So we're clear about that. I have no

problem with that. We'll try to find some alternative way to do it. That still leaves the question of whether there's something very close to the advance directive in a certain area, and that's what Alex focused on also.

PROFESSOR BACKLAR: Right.

CHAIR CHILDRESS: That will have to tie in more closely with what actually occurs in some areas.

PROFESSOR BACKLAR: And I go back to using the words that I'm very comfortable with, which is anticipatory planning.

DR. CASSELL: The whole thing is anticipatory. It seems to me that we're talking about two separate kinds of people. If we could separate them out, we would have an advantage. One has to do with a psychiatric patient who has a disease of fluctuating capacity, and also fluctuating clinical states. That's not at all unusual in medicine, even in patients who have no psychiatric disorder.

They sign up at the beginning of a research project and they give consent for the project, and good consent, and discusses what's going to happen in the possible stages of the disease.

They have given consent when they have the capacity to give that consent, and I don't see any fundamental difference--I'll come to what I think is one difference in a moment--between other medical states and the psychiatric disorders, in which case the person is not giving prospective consent, they are giving consent and the consent has to specifically cover that time when they might not want it.

However, we also know that this group of patients might not just wish -- when they are confused, agitated or extremely upset they might not simply not wish to take part, they might refuse to take part, and they have to be protected in both cases.

So we have added in a representative -- advance directive or advance consent. It's consent for research. If a patient comes onto a research unit in the agitated state, never has been seen before, that person does not qualify. They can't give consent. They shouldn't be used as a research subject. It hasn't been discussed with them when they are in a state when they could discuss what they think is in their own best interests.

I don't think a prospective aspect applies. I

think we have to make clear the consent for research, greater than minimal risk, requires a full discussion of what might occur, and so forth and so on, and also the protection which we already had in there.

Then we have this other problem where people who become permanently decisionally incapacitated, such as the dementias. They are the group that I can -- I can't think of another group, actually, where permanent incapacity is the issue.

There the idea that somebody may say in advance, I would like to be considered a part of research, I think that makes perfect sense also, although they, too, may have to be protected by a representative.

But we're not talking about advance directives, really. The name does matter. I think we ought to separate those two groups out clearly, otherwise -- it may be my confusion, that's why I'm saying all this, but otherwise we keep getting around to that problem. As far as this, I agree with Trish, the people like the dementias, they make a statement ahead.

Their care-givers, the people who are taking

care of them, may discuss it with them just like they discuss any other advanced aspect of their care, which they should assent to and sign to while they still have their capacity.

CHAIR CHILDRESS: Let's see if there are a few more comments around this part of the discussion. I know Alex has some others to get in as well. But what we'll do is, after getting more comments around this area we've talked about as advance directives, but with all the important qualifications in language and the situations to which this might apply, once we've done that, then we'll get Gary Ellis on on minimal risk and then we'll come back to some of these.

But anything else around this particular set of issues? Arturo?

DR. BRITO: I want to respond to something that Alex said. I agree with most of what he said, except at the end, I'm not sure. I might have misunderstood something, and I want you to clarify it, that concerns me a little bit.

When we're talking about greater than minimal risk, and I'm interested to hear what Gary Ellis has to say about that to clarify it a little bit for us, but

their major research has greater than minimal risk, that do not have obvious or immediate direct benefit to the patient, but may later prove useful for that patient, 10, 20 years down the line because of the findings of that study.

What concerns me is that blanket policy that does not permit consent for this type of research, even if it is above greater than minimal risk, it may actually prove to cause more harm in the long run. So I'm not sure.

Were you saying that if there is greater than minimal risk that there should be a -- and if there is no direct benefit, it's obvious -- I mean, after all, it is research so sometimes during the research process we find what the benefit can be. So are you saying that your opinion is that there should be no means for being able to consent for someone that can't make their own decisions for that?

MR. CAPRON: Well, I think, Arturo, this is the issue that we're all struggling with and, in part, is not an empirical question, as it was being posed yesterday, but it is a question about which information might cause us to refine how we go about it. That is

to say, how much research are we talking about, what kinds of things are at issue here? As a general matter, however, I was saying, more or less, what you heard me to say and what you may disagree with.

My experience in looking at human experimentation for the last, almost, 30 years is that the history of human experimentation is littered with victims of good intentions on people's part, too much enthusiasm for the value of the knowledge, the knowledge often not really quite as forthcoming, very often not as beneficial to the people it was supposed to benefit, and too much willingness -- the more disabled the subject is, the more different the subject is, to go ahead and do the research and have that thought that there may be some benefit there override a sense that this person is just being used.

I mean, I think that there are circumstances, extremely moving circumstances, in which a person with any kind of a disease, mental, physical, whatever, agrees to take on, on behalf of others, risks.

Sometimes great advances come and sometimes those are, as the mind run of science is, they don't add at that moment to anything that can be used, but it

was still a heroic thing for a person faced with that to do.

I think that we degrade that choice when we treat as though they are equally extraordinary gifts from people the use of other people who haven't made that choice and who have not said, faced with this, this is how I want my life to unfold, this is a sacrifice which I am prepared to make.

I mean, I think the people who do it, it's a supererogatory thing to do. It's not a required thing. We are not all required to be in science simply because we are, in a large sense, the beneficiaries of past researchers. It's a wonderful impulse. It's a grand thing to do that. It's a terrible thing when you do it under misimpression of what you are doing, but it's a grand thing to do when you do it --

DR. BRITO: I want to -- what I heard from the public testimony and from reading historically what has gone awry in research in the past, all the atrocious research endeavors, what I keep hearing over and over is not so much whether or not there's greater than minimal risk, whether or not the type of research necessarily, but the process in which it was done,

under deceit, to the person or the person taking care of that person.

In other words, I think that maybe if it's not so much we shouldn't be worried so much about -- I mean, of course we should worry about the risk involved, but maybe we should be concentrating a little bit more on the informed consent process and not be worried so much about saying this policy that you can't involve somebody in research -- you could involve somebody that has a valid representative in research if it is clearly explained and it is clearly understood that there may not be a direct benefit to that person. Once again, therapeutic misconception, that's the common problem in research, it is not explained whether or not you're decisionally impaired.

MR. CAPRON: Well, I agree with just about everything you've said. I guess I just draw the limit on the authority of the surrogate to make a decision which has not been in some sense also chosen.

Now, we're talking about these advance directive sorts of things, we're getting away from the term if we can, but the choice is a generalized choice. It would not, itself, meet the requirements for

informed consent but it is some sort -- what I'm looking for is some sort of commitment from that person to say, I'm in Category A rather than Category B.

I'm in the category of people who -- I'm willing to make a sacrifice. And without that, I'm not comfortable with the surrogate doing that. It just seems to me -- and I entirely do -- one of the things you've said.

For most of what we're talking about, the important issues are avoiding deception, avoiding the therapeutic misconception, and other things where people go into something think that they're doing X when they're really doing Y, because there hasn't been good communication.

I entirely agree, and I think Laurie said this before and I agree with her about that. We need more attention to that issue throughout all our research stuff and in our document still. But there's still this residual category.

CHAIR CHILDRESS: Okay. We'll get Laurie, then let Alex respond, then we'll turn to Gary Ellis and we'll obviously come back to these issues.

MS. FLYNN: This has been very, very helpful,

I think, and I think we have identified clearly that box, if you will, in which we have some concern and some difference of view.

Just two thoughts. One, I do want to stress again my concern that we may want to look at, because of the issues of those who may really not be able, by virtue of their illness, to ever give fully informed consent or participate in the ways we would like to see strengthened, I would look to surrogacy, particularly in terms of someone who has durable power of attorney or who is a guardian as something to be explored for research that is a minor increase over minimal risk, and this includes a vast array of things like PET scans. These are not intrusive, these are not risky in the sense that many of us may be thinking about. One needs to ask ourselves whether our perception of this and the research enterprise has been unduly skewed by some of the kinds of testimony that we heard.

We did indeed hear, and we need to pay close attention to, allegations of abuses in psychiatric or other research. There clearly is a very vulnerable subject population here and there clearly have been significant abuses.

But we don't know anything yet about the scope, the scale, the standard that's out there. We really may be over-responding and thereby preventing some important research and the benefits of that research.

That's why I think there is an empirical issue here, as well as perhaps the value of looking again at some work I think the Alzheimer's people have done, developing more of a sliding scale, looking at a little bit more of a complex layout that increases the protections and supports for the individuals as the increases in risk advance.

So I wonder if we might be helped as we think through this with the different kinds of subject populations and the different degrees of risk, which again, we all need to hear more from Gary about.

CHAIR CHILDRESS: Jonathan?

DR. MORENO: Could I just point out that the current framework does permit potentially beneficial diagnostic studies to be permitted, or consent, if you will, by a legally authorized representative. PET scans could be beneficial to the subject, insofar as they are a monitoring procedure.

MS. FLYNN: Well, I guess one would need to discuss what we mean when we say diagnostic study. If it's diagnostic to the individual --

DR. MORENO: Yes.

MS. FLYNN: -- that's not the only way in which those studies are valuable. Those studies look at the basic interactions going on in mental disorders and they may or may not directly benefit that individual, but they clearly benefit the advance of knowledge about what goes on with --

DR. MORENO: Sure. I've heard them described as also a potential benefit to an individual subject.

DR. DUMAS: I don't think there's any research project where anyone knows a priori that it's definitely going to benefit the subject, because you don't know, a priori, what the findings are going to be. So there is no situation in which we can assure people that they are going to be directly benefitted from this research.

I think that in the case of people who have difficulty or some impairment in making decisions where there is greater than minimal risk, we have to have appropriate protections.

We are disagreeing about what those protections should be, but I worry about using people in that category because of the very reason that we are having to spend this time with this population: they have been exploited. And I want to make sure that we have guidelines that will minimize the possibility of that type of exploitation.

Now, we know that it happens and we know it's continuing to happen, even among people who try or who think that they have made provisions to protect. So I don't think that we can be too zealous in our efforts to impose some limits on how human subjects are used, and under what conditions, for research.

CHAIR CHILDRESS: Okay. We'll get Trish, and see if Alex wants to say anything in response, then we'll turn to Gary.

PROFESSOR BACKLAR: I just want to remind us about the limits of consent and why we're so eager to put protections in place with any population.

MR. CAPRON: One further concern, Jonathan, also on page 123, where you talk about one of the other objections to advance directives. Then you go on and say that it may be necessary for the states, if this

became part of regulation, to adopt legislation. If what we are talking about is something in the category of a prospective consent, I hope we'll be very clear that, for something of that sort, one really doesn't need --

DR. MORENO: Right.

MR. CAPRON: Yes. And I think that that doesn't come through here and it sounds as though that would be a problem. I'm going to hold my other comments, because we've been trying to get to Gary for quite a while.

CHAIR CHILDRESS: All right. Let me just mention, what Alex is proposing in terms of some detailed alteration, we really need to do this as individuals now, let's say in the next few weeks. This report has been a long time in gestation. We've had discussions surrounding it.

There are clearly some other things we need to do in terms of getting additional information, but we also need to be working over this draft very, very carefully, making sure that we get the changes in that we think are important.

Jonathan is putting those in bold, so the next

time we look at this we can check and see if Alex has proposed something on page 123, that it's been incorporated, and then we can see very quickly, well, wait a minute, we don't like the way that's going.

But we really have to do that, otherwise we won't be able to bring this to a close. So this is for future steps or further steps. Let's commit ourselves to doing that over the next two weeks so we can really bring this to closure.

DR. CASSELL: Will we see any changes as a result of this meeting before we do that, or will we --

CHAIR CHILDRESS: Oh, I think you should -- no, no. You see, basically, other than the discussion we've had right here we haven't had a lot of discussion of the text.

DR. CASSELL: It seems like -- you're in trouble now.

MS. FLYNN: Jim, don't -- tried to incorporate the NIH's group's views. They have not yet been articulated for us, but I think there was some substantial expertise there. A useful review of that material might also enrich our --

CHAIR CHILDRESS: Two things. One, is a lot

of that has already been incorporated. Arturo, Diane, Trish, I, Jonathan, and Eric, and Henrietta--did I catch everyone there--met for a good while after that conference.

Actually, if you go back and look at the bold, particularly in the early parts of this, you will see a lot of that already reflected. So we did a lot of that. However, we will have in a few weeks a fuller statement from that conference, and we'll want to make sure that we've incorporated and attended to what's --

Now, the bottom line was, no further regulation. We are apparently going to make some recommendations in the area of regulation. Is it urgent? No. We can hold off.

Okay. We are glad to welcome Gary Ellis to help us think about minimal risk. We're always glad to have you help us clarify matters. Thank you for joining us.

REGULATORY UNDERSTANDING OF MINIMAL RISK

Discussion: Gary Ellis, Ph.D.

DR. ELLIS: Thank you, Mr. Chairman. Good morning.

Can I have the slides on, please?

I'm going to respond to the question that, you asked me to define and describe the regulatory view of minimal risk. In order to do that, I need to give some background as to when the term applies, who applies the term, and you'll recognize that this is because of the structure of regulation that we have.

(Showing of slides.)

DR. ELLIS: So the Federal policy for protection of human subjects contains the term minimal risk and it is defined, so it applies to 17 government department and agencies' research portfolios.

(Changing of slides.)

DR. ELLIS: Similarly, the regulations of the Food and Drug Administration contain the term. It is defined in the exact same way as the Federal policy for protection of human subjects.

(Changing of slides.)

DR. ELLIS: And so the term minimal risk that

I'm going to use and define applies to research funded by any of 17 departments or agencies, regulated by the Food and Drug Administration, or voluntarily pledged to the regulations of the Department of Health and Human Services.

(Changing of slides.)

DR. ELLIS: There is no mandate that is applied to research not conducted by the aforementioned departments or agencies not regulated by FDA or not pledged to 45 CFR 46. This is very important. You've heard me say this before, you've seen these slides before. You heard Alex describe these yesterday. It's very, very important.

(Changing of slides.)

DR. ELLIS: Minimal risk means--this is the regulatory definition--that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life, or during the performance of routine physical or psychological examinations or tests. That's the black-and-white definition and it's been more or less unchanged since 1981. It was changed in a minor way in 1991.

Now, who applies this definition? In general, a quorum of the Institutional Review Board applies this definition. So in any case, that is at least three individuals, which must include a non-scientist.

So again, minimal risk is not the judgment of any one individual, ordinarily, it's the judgment of at least three individuals, one of whom must be a non-scientist, by regulation, in the domain of research that I described. Beyond the domain of research that I described, none of this necessarily pertains.

Let me stop there and say that I think that in practice the way that minimal risk is applied is, IRB members know it when they see it. I'm not certain that too many IRB members -- well, I shouldn't speculate.

We don't know if IRB members could quote this definition, we don't know if they could pull it out on a laminated pocket card, but we are confident that they know minimal risk when they see it. Perhaps they could not explain it in the terms of this definition, but they bring their good sense to the table and they have a feel for what is greater than minimal risk.

I'll give you an example so this is less abstract. Let's suppose that you, as IRB members, are

considering a protocol that involves lumbar puncture. So you may have a visceral reaction and just determine in your mind that lumbar puncture is greater than minimal risk, or you may ask some questions or seek information, what are the risks of lumbar puncture itself.

I think physicians or health care professionals might say, well, there's the risk of infection, there's the risk of nerve damage, there's the risk of headache from upsetting the cerebrospinal fluid, and the extreme risk of paralysis.

Others who are physicians may agree or disagree with that list, but that would be a reasonable thought process for an IRB member to go through. Then there is a judgment.

So this is a more sophisticated judgment than the first judgment I described, which was a visceral response to everything you know, or think you know, about lumbar puncture.

Now, you have specific risks of harm or discomfort attached to the research procedure and you make a judgment as to whether the probability and magnitude of those four specific harms or discomforts

are greater than they are in daily life. Let me go forward.

(Changing of slides.)

DR. ELLIS: On this slide I have not added to, nor subtracted from, the definition of minimal risk, I've just displayed it in a different way so that we can work through what the more sophisticated IRB members or analysts might actually work through.

On the left side of the not greater than side, it says, "the probability and magnitude of specific harms or discomforts in the research," so this is not abstract.

You are now, as IRB members, considering a specific research protocol and we can know, or at least estimate, what the specific harms or discomforts conveyed by this research might be. Then we can estimate the probability and magnitude of each of those harms or discomforts.

Then we would compare, and I'm moving to the right side of the equation, and we ask the question, is the probability and magnitude of these specific harms or discomforts not greater than the probability and magnitude of those specific harms or discomforts in

daily life or in routine exams or tests?

If you conclude that that probability on the left is not greater than the probability on the right, then you would have something -- a proposed research is not greater than minimal risk.

One remaining question on the right side of the equation. It says, "in daily life," and so you may have the question, in the daily life of whom? It's not stated in the regulation. The regulation says just what it says on the slide, "in daily life."

Now, I know it's not the daily life of healthy persons, because that trial balloon was floated in the 1991 rule making process and the term "healthy persons" was explicitly omitted from the rule. So this, we know.

Well, is it the daily life of patients, is it the daily life of people who may be less than healthy? One could proceed under that interpretation but it would lead one to the conclusion that people who are in harm or discomfort, the patients, can actually be subjected to greater harm or discomfort than another ordinary person. And that would be, I submit to you, an unacceptable conclusion.

Let me restate that. If you proceed with that interpretation and on the right side of the equation you have the person in extremis, you could do just about anything to that person and you'd come to the algebraic conclusion that this is not greater than minimal risk because the person is in such bad shape anyway. That would not be a positive conclusion for the protection of human subjects and research.

So our office prefers to interpret the concept of daily life as meaning the daily life of all people, which includes the research subjects, which includes healthy people, includes people who are less than healthy.

So if you proceed in that manner, you would not ever come to the conclusion that you can inflict harms or discomforts on people who are in considerable harm or discomfort because it's no worse than they are anyway, and it would be most protective for human subjects.

So to conclude, I just want to restate what others around the table have said before me, using different words. Minimal risk is not moderate risk, it's not intermediate risk, it's not medium risk, it's

not midway risk, it's not so-so risk. We take minimal to mean least, smallest, limited, minor. Minimal risk is just what it means, minimal. So this is a narrow category of research that is, as it says, minimal risk.

I'll be glad to answer any questions you may have.

CHAIR CHILDRESS: Thanks very much, Gary.

Trish?

PROFESSOR BACKLAR: Thank you, Gary. I'm a little confused. You're saying that this risk is not experienced by healthy people. Are you saying they're ordinary?

DR. ELLIS: I'm saying all people, which includes healthy people, less than healthy people, subjects of research. That's what I'm saying.

PROFESSOR BACKLAR: All right.

DR. ELLIS: I know that it's not the daily life of healthy people. This I know, because that term was explicitly omitted after being floated as a trial balloon in 1981.

PROFESSOR BACKLAR: Then would you say, using your example of a lumbar puncture, that this would not be minimal risk, since most of us don't experience this

in our day to day lives?

DR. ELLIS: I think four out of five people would conclude that lumbar puncture is greater than minimal risk. I think there may be a commissioner or two here who would disagree with that. Perhaps not.

PROFESSOR BACKLAR: How would you deal with this then if you're doing research on somebody who, for instance, has schizophrenia and their risks of their everyday life are far greater than yours and mine. So what kind of baseline do you have in mind here, because it's still a little bit fuzzy for me in the way you've described it.

I had in mind that it would be ordinary people so that if one were going to describe risk of somebody in a population, for instance, someone who suffers from schizophrenia, right away you would be able to -- the very fact that they're being in research, may be for them riskier than it would be for you.

DR. ELLIS: Let me answer twice, first in lay terms and lay language from instinct. I know that I can't come to the conclusion that, because the person has schizophrenia and is in worse shape in some ways than the healthy person, that I could do more to that

person or with that person than I would with a healthy person. So I don't think I used any regulatory terms there and I announced I was speaking in lay terms from instinct.

Now let me speak as a regulator. If I look at this equation and I say, what is the probability of magnitude of harm or discomfort in the research on the left side of the equation, I suppose I could put the individual with schizophrenia, the prospective subject with schizophrenia, on the left side of the equation and say, well, what's the probability of magnitude of harm or discomfort X, Y or Z for this schizophrenic patient? That's one way to work that person into this equation.

But I would avoid putting the individual with schizophrenia on the right side of the equation and saying in the daily life of the schizophrenia, because that could lead me to the conclusion that, in my first statement, I found unacceptable.

CHAIR CHILDRESS: Diane?

DR. SCOTT-JONES: Gary, I have a question about your reference to the daily life of all people. That sounds as if the point to which you would compare

the person who's a prospective research participant is an average, and then you are then referring to healthy persons, aren't you? It seems that in the end the standard is the healthy person. If you're saying all people and then you somehow take an average of all people, that would be a healthy person.

DR. ELLIS: If your assumption is that the average person is fully healthy, then I would disagree with your assumption. I think that, if I look at all people, that the probability and magnitude of harm or discomfort X, Y or Z, is real and is measurable in some number of those people. So you and I might be at odds as to whether, with regard to the probability and magnitude of specific harms or discomforts, an average person equals a healthy person.

DR. SCOTT-JONES: Well, it seems that the definition is fraught with problems as long as it stands the way it is. Is there the expectation then that the decision rightfully belongs with individual researchers, with specific IRBs? Because it seems that as long as the definition remains this way you will always have instances in which you need to discuss particular cases to decide whether there is minimal

risk, a minor increase over it, an increase over it. It seems that there is no way out of the problems that exist with this definition.

DR. ELLIS: Let me give some background again on the purpose to which this definition, this term, is used in the regulations. You maybe overestimate the problem or you may be looking to the concept of minimal risk to add a use to the term for which it wasn't intended.

The term "minimal risk" is used in the Federal Policy for Protection of Human Subjects, in the common rule, essentially for three purposes. One, as a cleaver to decide what can be reviewed by other than a fully convened IRB. I'm talking about an expedited review process. So that's one important use of the concept of minimal risk.

Research that's greater than minimal risk not be found on a list of 10 items must be reviewed by the fully convened IRB. So, as you say, it must be discussed.

Minimal risk is also used as a cleaver to decide what research can proceed without consent. And minimal risk is also used as a cleaver to decide when

documentation, a consent form, may be omitted. So those are the three principal uses in the common rule.

There's another minor use. One element of informed consent says, for research greater than minimal risk, certain information must be conveyed to the subject. But I've described the three main uses of the concept of minimal risk.

If you are looking for a cleaver for other purposes, I guess there's two choices. One, is to redefine minimal risk. I don't know that I would advocate that. The other, is to invent some new cleaver to serve your purpose.

CHAIR CHILDRESS: Alex.

MR. CAPRON: I guess my hope in having you make the presentation today would be that we would get some sense of whether there has developed a kind of a common law of this. That is to say, that in the IRB guidebooks, in IRB educational materials, we have a fairly rich set of examples of the sorts of things that if you were called for your advice and someone said, well, we have a questionnaire for someone to fill out, well, is it a sensitive subject? No, it's not a sensitive subject. Well, that's an example of

something that's not --

You're going to do a needle prick to get a little blood. Is that? No, that's not. In other words, we're going to do venipuncture. Through the years, all the different kinds of things that are done. Is there any sense of the way in which that term is filled out?

I mean, there are many terms that the law uses, the reasonable person and so forth, that remain sort of, each case, a matter of the decision of the jury. There are outer limits where judges will say that something is, on its face, negligent and no reasonable person would have done that.

But the term remains elastic. There are other terms which become terms of art where we have, through case law and so forth, a sense of where you could say, well, what does consideration mean here or something.

Where are we on this? I guess I was assuming that part of your presentation might be that you could really give us a sense, particularly as it relates to the kind of impaired subjects we're talking about here, where the minimal risk line would likely be drawn, recognizing, as you say, that, strictly speaking, it's

a decision of the majority of any IRB. Or it may be, in some cases, the IRB administrator or IRB chair who says, I sign off on this, through expedited review; I'm convinced that it meets the minimal risk.

DR. ELLIS: Well, I understand the question. I have no slide. I was going to show a blank slide to illustrate that I have no answer for the question, but that didn't work.

(Laughter)

MR. CAPRON: Important data showed up on this slide, so I can't do it.

DR. ELLIS: Alex is asking for the frequency distribution, where we have arrayed ordinary research procedures that repeat over and over through the years and around the country, a labeling on that frequency distribution of how often an IRB found this to be not greater than minimal risk, or greater.

That information was not something that's ever been collected, so there is -- let's call it a folklore. It's not even as formal as the common law. I think that at the extremes there would be 100 percent agreement among IRB members, probably among researchers, among observers, that a needle prick at

one end, or something dramatic at the other, is either less than minimal risk or greater. In the middle, IRBs will come to different judgments. On lumbar puncture I thought I could split this group, but nobody spoke up.

So the best that we can do as administrators of this large system is to say, well, we're going to put the judgment, under ordinary circumstances, on at least three people who are close to and understand the research site, which means the researchers, the expertise, the prevailing values and ethics of the community. That's as far as we've gone, is just to say, well, we trust that system. That's the best that we can do.

Now, why haven't we collected data on that system, is a good question. We heard before that there is a general lack of evaluation of the system. Dr. McKay came before you in January of 1997 and said he'd be back in March 1997 with a results of a 191-question survey, and I for one am still very anxious to see the results of that.

MR. CAPRON: Right. This wasn't -- let me be clear. In raising this this way, this was not in the least a statement on my part of reminding us that we

have so little data about the system.

I actually thought that, through your educational programs and so forth -- I mean, you get -- IRBs are not plants that grow in the jungle, they are groups of people who go through processes.

Part of those processes, as you suggest, are local processes and then part of them are educational processes. So if you have new members of the IRB you are more likely to want to have them do an educational program so they get their bearings. And I just wondered what the bearings here were. I thought there might be something at that level. There was one other thing, but there's not, so I'm dropping that.

There's one other thing that surprised me, what you said, and I may have misunderstood you. When you were looking at the chart that you have up here, you were asking that the -- you were thinking that the IRB would be comparing the magnitude and probability of specific harms or discomforts that arose in the procedure with those same likelihood -- the probability and the magnitude of those same things arising in ordinary life. That surprised me, from just my own experience with IRBs over the years, is the sense that

I had always observed what seemed to me to be more of a trade-off.

That is to say, well, what's the probability that people fall, break their legs, ski into trees, whatever it is? I think that that's sort of a distribution. And those risks of dying unexpectedly, being injured unexpectedly, and so forth, are the risks of daily life.

Now, one may object that, unlike average income, it doesn't make a lot of sense to talk about those as, what is the average person here, because the distribution is so dramatic. It's sort of like average income in a country in which there's a very unequal distribution of income, a lot of very poor people and a few very rich. Is the average income $20,000 or should we really be drawing on something else?

But, I mean, I took that to be some way in which we can say, well, what are the probabilities you're going to have some bad thing happen to you? But not that you would specifically have the same bad things happen to you that you would have from the research.

That is to say, what's the probability that

you will have a headache or be paralyzed, which are the two major risks of lumbar puncture, but is the kind of discomfort generally or the kind of risks generally there more than what happens to people, on average, in ordinary life?

That's what I thought was going on. But you seem to say, no, it's really, you're looking for these specific risks and saying, do those happen to the average person in ordinary life. Did I understand you correctly?

DR. ELLIS: You understood me correctly.

MR. CAPRON: Is there some regulatory explanation, I mean, some commentary of an official sort that OPRR or others give to tell people that that's how they're supposed to read this?

DR. ELLIS: I've shown this slide several times.

(Showing slide.)

DR. ELLIS: I don't think there's any commentary beyond this. I think what you say, actually, is probably quite true, is that most IRB members, for the right side of the equation, use a more vague or a more grand average of daily life. And I'm

not disagreeing with that.

In fact, that was the sense of my opening remarks, is that I think most people sort of apply this by instinct and never get to this slide at all. But if we sit down and we try to map out what this black-and-white letter of the regulations say, I think you would actually map it the way that I did.

Obviously, I sat down to map it and I came up with that next slide. You may disagree. I think, in practice, most IRB members actually never think that specifically about the risk of harm or discomfort X, Y or Z in daily life.

MR. CAPRON: Yes. I mean, the phrase there "harm or discomfort," to me, is different than the phrase "the harms and the discomforts anticipated in this research." Harm and discomfort are like pain and suffering, they are broad categories. But, I mean, I'm not arguing that your interpretation is wrong. Again, you're in an official position to interpret and I'm not.

What I'm sort of wondering is, what do we bring in? If we're using that term here, I hate to use the term again, common law, but what sort of received

understanding do we bring in here?

Yours would be one which I would expect to be a very influential received understanding, particularly if it's been reduced to writing, if it's been used in IRB educational materials and lectures and so forth, it's likely to influence the way our IRBs go about their business.

I mean, in my own sense, going back to the Daumel paper, Daumel was -- correct me on that paper; I can't remember. But way back in the time of the National Commission, there was a paper published in the *New England Journal* which looked at research and argued that most research, in fact, does not have greater risks than ordinary life.

And they were not just looking at the research, the occurrence of specific incidences of research, and saying, do those things occur. They were looking generally, as I recall the article, at the risks of ordinary life. They had some broad statements about risks of accidents and so forth.

I've always understood the term to be derived from that source and to reflect that very, as you say, sort of generalized understanding of what are the risks

and discomforts of ordinary life.

CHAIR CHILDRESS: Okay. I have Eric, then Arturo.

DR. CASSELL: I don't want to tie too much into this, but the definition says, "Ordinarily encountered in daily life -- extraordinary -- of a risk, the population we're talking about now does not have the usual perception of the world around them because they are sick.

So our problem is that what we consider to be an ordinary risk, clinical risk, like a physical examination, may be seen by somebody who -- our problem is how to -- outside of them at the same time recognizing -- so we have a minimal risk category, but we also try to protect them --

CHAIR CHILDRESS: Gary, did you want to respond?

DR. ELLIS: No.

CHAIR CHILDRESS: Arturo?

DR. BRITO: I've been trying to assist the debate throughout the hearings. I'm one of those people who feels that lumbar puncture is really not much, if at all, minimal risk if it's done in a correct

fashion and in the right hands.

When you were initially describing the four different risk factors of doing a lumbar puncture I thought your point was going to be that, in ordinary life, your chances of getting an infection are going to be greater than in all the lumbar punctures that have ever been done, in a percentage.

Your chances of getting paralyzed are going to be greater than all of the people who have ever been paralyzed secondary to lumbar puncture, even in research -- especially in research protocols. You obviously made the other point.

So I'm thinking more of percentages. I'll give you an example of something that is considered minimal risk by most, is venipuncture. They showed in studies that children that have had venipunctures in research protocols, by far, suffer less psychological consequences of having that venipuncture than those that had it in clinical circumstances.

So the point there is, in ordinary life, somewhere down the line you're going to get your blood drawn, probably. The research, by doing it in a research protocol, it actually reduces the chance of

any harm being done.

My point here is, and this is what I was trying to say earlier, that it is so difficult to make a blanket statement or draw the line somewhere of what is minimal and what is moderate. In certain situations, something that appears to be higher than minimal risk may actually be minimal risk.

I think I heard Laurie say earlier, somewhere we have to maybe describe a bit more in the sense of gradient and be very careful in not excluding people from research studies that may involve them in what appears to be something that's greater than minimal risk.

CHAIR CHILDRESS: Other questions, comments?

MR. CAPRON: I don't disagree with that, but I want to underline one thing that the discussion has made clear to me. Which is, if we begin moving away from the standard that we have and the draft as it now is and we start saying, well, when there is only minimal increment to minimal risk, we are adding on a vague notion on top of a notion which, as written here, I think is almost incoherent as it is now being applied and obvious has a utility, and it can be used and is

used all the time by IRBs, but it's not a very fixed point.

It isn't like average income, the average household income of the United States. What we can say is, that is $28,272, and a moderate increase over that would be $2,000 or less. That's moderate.

DR. BRITO: As we begin to draw additional categories on something that is as vague as this, we're beginning there -- I would agree with all the comments yesterday when people were saying don't make too many categories, because we're making categories which are like wet spaghetti. I mean, it's just --

DR. BRITO: Exactly. So I guess what I'm saying is, let's not make the categories. I think the effort should be more concentrated on the informed consent process and the explanation and communication, et cetera.

I think it's impossible to make these categories. I mean, somebody even mentioned PET scans. Well, someone else may say, well, the psychological harm that can come from that is much greater than minimal risk.

So there are just so many interpretations you

can have from that, whereas somebody else -- you know, I would consider it no big deal for myself, but someone else, particularly somebody who has a psychiatric disorder, may suffer even worse by being put through a PET scan. So the point is, I think we have to be very careful not to categorize it so neatly because I don't think it can be so neatly categorized.

CHAIR CHILDRESS: Diane, then Jon.

DR. SCOTT-JONES: We have a big problem in getting this report done, because we have a notation on page 143 from Jonathan that we need to decide what we're going to say in this particular report about minimal risk.

I think we may have a problem that may be practically unresolvable if we're required to use the definition of minimal risk that's there, because it implies a quantitative judgment, as Eric has just pointed out to us.

From what Gary has said, in practice, people make a qualitative judgment. That is, they recognize what minimal risk is, what greater than minimal risk is in an intuitive way, and they're making a qualitative judgment that they couldn't quantify if their lives

depended on it.

So we're treating this as if we can somehow make a quantitative judgment and talk about increase over minimal risk, a minor increment. Those are all quantitative terms and we are not able to do that.

Also, the notion of daily life in that context is absurd, given that Americans' daily lives vary so dramatically, with some people on a daily basis being exposed to enormous risks, ranging from gunshots to being run over by a truck; other people's lives are more sheltered and they're more protected.

So we are just being irresponsible if we say, well, it's all Americans' daily lives, when any person knows that some Americans' lives are extraordinarily poor and other Americans' daily lives are wonderfully protected and safe.

So I think we have two big problems. One, is we are jumping from qualitative to quantitative judgments, and the other is that we are imagining that Americans have some homogeneous life that is relatively benign or an ideal life when, in fact, that's not the case. We need to do something about this definition.

CHAIR CHILDRESS: I don't disagree, but we

have to ask what we can do for purposes of this report. To do something with it in the larger sense, in terms of trying to change the common rule or, a much slower process, helping to change the interpretation of this particular category in the common rule, I think we will all be dead before we finish this report.

DR. MORENO: Gary, I sometimes wonder what would happen if the definition dropped the first disjunct which is the one that everybody always talks about, namely, those ordinarily encountered in daily life, and only use the second disjunct to the right side of the -- namely, the performance of routine physical or psychological examinations or tests.

In other words, part of my question may have to do with what you understand as a regulator to be the nature of the "or." Is that, first of all, an exclusive "or" as logicians say, in other words, it's one or the other but not both, or is it an inclusive "or," "and/or," as we recognize in ordinary English? In either case -- well, if it's the former, then might not IRBs be able to decide which criteria they would like to apply?

It seems to me, to take the example of the LP,

that lumbar punctures might qualify under the left side of a disjunct, but probably would not qualify under the right side. That is to say, I don't think that lumbar puncture is part of a routine physical examination, at least I don't want to go to a doctor that says it's routine.

So then my question is, I guess, several-fold. How much flexibility -- in your view, do IRBs have in deciding which disjunct to apply? Materially, what would be gained or lost if one were to use only the second disjunct?

DR. ELLIS: Well, I can answer your question as a matter of reading the plain English. The clause, the "or," to use your words, I think, is exclusive, meaning A or B, it's not an "and," it's an "or."

DR. MORENO: Ordinary English is usually taken to be inclusive. So in other words, in order to make it --

DR. ELLIS: Let me put it this way. You can have one or the other.

DR. MORENO: But not both.

DR. ELLIS: You don't need both.

DR. SCOTT-JONES: But you could have both.

DR. ELLIS: You could.

DR. MORENO: In ordinary English, usually to make it exclusive people say either A or B.

DR. ELLIS: Yes. I read it as "or," not "and," because it would say "and" if it was intended to be "and."

DR. MORENO: Well, it would say "and/or."

DR. ELLIS: But it doesn't say "and/or," it says "or."

DR. MORENO: So you consider it to be exclusive.

DR. ELLIS: Let me go back to my first point. I think that minimal risk and greater than minimal risk is what a majority of the quorum of the IRB finds to be greater than minimal risk.

MR. CAPRON: Why isn't the IRB administering -- excuse me. Into the microphone. If you're dealing with expedited review, isn't that usually something that the chair signs off on? I don't --

DR. ELLIS: If you're dealing with expedited review, yes.

MR. CAPRON: Well, that is, in my good sense, the major use of it. Yes, if it was occasionally used

to avoid the documentation for consent, you're doing a face to face interview with people in public places and you don't make them sign a consent form. Why? Because you're asking them questions which are not risky to them. Occasionally you do that research without any consent at all because you're doing observational studies. The major use is expedited review.

DR. ELLIS: I think you're correct.

MR. CAPRON: And that can be done because the chair signs off, it wasn't more than minimal risk. I sign off and I approve it for the IRB. So you don't need a majority. You could have a single physician, the chair of the committee, looks at the lumbar puncture and says, this is not more than minimal risk.

DR. ELLIS: No, that's incorrect because lumbar puncture isn't on the list of 10 categories for expedited --

Let me go back to the main point, that the IRB, in its wisdom, under certain circumstances a single member of the IRB, as Alex points out, for certain procedures that are listed determines what is greater than minimal risk.

Now, those individuals do that with reference to this stated standard and I don't think, in practice, that there's the level of dissection of this stated standard that we've just gone through around the table, in all honesty.

So if you are interested, for a certain population of prospective research subjects in creating a cleaver, is the word I've used, to decide what research can proceed, what research can proceed under certain circumstances, you may wish to create some new term, some new definition for that term that serves that purpose because the purpose of this term, as Alex has described, is mostly to determine what can go forward for expedited review secondarily, tertiarily, when consent can be omitted, when documentation of consent can be omitted for research that is covered by the Federal departments, policy, regulated by the FDA or voluntarily pledged. So you still have the issue of research beyond that.

CHAIR CHILDRESS: Are there any other comments? I know Trish is waiting to get in.

PROFESSOR BACKLAR: Well, the problem is, I see that we can't seem to get away from this, indeed,

rather relative concept, the way it's dealt with. It's an interesting idea, Jonathan, that you brought up about, which side of the "or."

If you went to the physical exam, would that be for a healthy person or would it be -- in the same box? I think the real problem is that average person as opposed to the healthy person.

If you had a healthy person, would that give us a clearer baseline through which we could then go into, depending on the population that you're dealing with, that somebody, for instance, again, with schizophrenia maybe having a PET scan might be more difficult than it would be for me to have a PET scan.

CHAIR CHILDRESS: Rhetaugh?

DR. DUMAS: I think our dilemma lies in the tendency to be too specific or to try to go to a higher level of specificity than is possible in situations such as the ones that we're discussing.

It might be that what we need to do is to think in terms of parameters and general principles. I've said this before. There are some things that must necessarily be left to the judgment of the people who are making that decision, and the best that we can do

is to give them some guidelines for making the decision, not to make the decision for them. Now, that's one of the points.

The other has to do with the same kind of thing about the report. I don't think that we are going to come to agreement on all aspects of the content of the report, but I think we do need to agree on the basic points that we want the report to reveal.

If we could do that, the most important points that we want to make in that report, we could come to a decision on that, then we would have to leave it to the writer to convey that. I don't think that we could get all mixed up in the context of this because we'll never finish it.

CHAIR CHILDRESS: Any last comments for Gary?

MR. CAPRON: I'm sympathetic with the point that Rhetaugh just made. This is really one of the fulcrum issues of this entire report because, and I sense there is a division, a division which may be dramatic in the sense that we may have an 8-10 vote on the Commission, one way or the other, as to whether or not it makes sense to say, because of the value of the research process and the potential findings from

research, we want to allow research to go ahead without the consent of the individual, with someone else's consent--I mean, we are still talking about other protections; there would be an IRB reviewing it, there would be some surrogate decision maker--which involves more than minimal risk. So it then becomes important that we have some sense of what we're talking about there.

DR. BRITO: But parameters determined by whom?

DR. ELLIS: Well, it is going to be determined by the IRB. But there are limits to what IRBs can determine, and there may be -- I'll put it this way.

If we discover there is not a common understanding that within the context of this report we should go into some detail, and the writing we'll leave to others, Rhetaugh, I agree, but we should have a discussion of the kinds of things that we believe that term to mean when we use it here, otherwise we haven't said anything.

DR. SCOTT-JONES: Could I very strongly agree with what Alex just said? I think we have to decide, even if it's no more than saying that these are problematic, but this is how we're using the term. I

believe we have to have some statement in this report or what we have said is going to be meaningless.

I think a definition that is left wide open allows for the possibility of mischief when that definition is used in the real world and people are trying to get a research project under way and stay on schedule.

I think we have to aim for as much clarity and agreement as we can muster among ourselves. I think this is critical. We cannot just use language to avoid the problem of deciding what we need to say.

PROFESSOR BACKLAR: Right. We have to have some kind of baseline that is understood.

DR. DUMAS: But you can't exhaust all the possibilities that would fall under that category.

DR. SCOTT-JONES: Right. I agree.

CHAIR CHILDRESS: Jonathan, then we're going to move to a break.

DR. MORENO: At the risk of repeating myself, this draft attempts to deal with this problem by establishing some examples of minimal risk and greater than minimal risk interventions--not research, interventions--for these kinds of populations.

The language is on page 146. It's Number 6. We can tweak that for a while as a group, or individually, if you like. There is discussion around pages 90, 91, 92 on this issue. So it doesn't seem to me that there is no basis for this discussion in the current draft.

CHAIR CHILDRESS: And what I would urge is that we all look very, very carefully at this and, not that we'll have a chance to do it thoroughly today, but decide exactly how we want to proceed. It may well be that we'll look carefully at this, and a couple of people who have paid a lot of attention to the debate about minimal risk, for example, Alex and anyone else who would like to join in, might propose additional language for our consideration.

Bette gets the last comment and we'll take a break.

MS. KRAMER: I hate to take the last comment, but I thought it might be helpful to the committee to hear from somebody who is listening to the discussion for the first time.

As I've listened to you, and having read the report just recently for the first time, I think that

the reality is that what you're talking about, just plain and simple, does not permit an objective measurement.

Therefore, it really becomes a question of trust and, you know, how paranoid do you really want to be? I think if you believe it's appropriate to be totally paranoid, then you just don't allow any research at all to go forward where you can't get a true informed consent from the potential subject, and otherwise I think you have to rely on the nature and the character of the narrative.

And, as I said, having read the report for the first time, looking at it fresh as opposed to having reworked it and reworked it, and listening to discussions, I really want to compliment you all on it. I think it's beautifully written. I think it expresses great sensitivity. I think it's a document that, in general, the Commission can really be proud of.

CHAIR CHILDRESS: Okay. Thank you, Gary, for joining us. We appreciate your help. Okay.

Let's take a 15-minute break and resume.

(Whereupon, at 10:00 a.m., the meeting was recessed.)

AFTER RECESS

(10:17 a.m.)

DISCUSSION CONTINUES ON RESEARCH WITH DECISIONALLY IMPAIRED SUBJECTS: DRAFT REPORT

CHAIR CHILDRESS: Okay. Let's get started again. Okay. Jonathan wants to say something.

DR. MORENO: Just very briefly. I just spoke a few minutes ago to a relevant section of the report that speaks to attempting to array examples of minimal and greater than minimal risk, is not on pages in the 90s, it's in the 70s. It starts on page 73 and goes on for about 8 or 10 pages.

CHAIR CHILDRESS: Let's pick up our discussion and see if there's anything else you want to say about minimal risk. We've noted that the problems, the difficulties, in defining it and specifying it. What I would urge people to do, since this does play a crucial role in the document as you have it, is actually to look over those pages very, very carefully and let's do some e-mail exchanges.

I mean, let's really now pick up along the lines of the cloning report, movement toward modifying

this in a way that can get us to a final draft. Those who feel particularly strongly about things, let's come forward with proposed language and let's move it.

Now, connected with that, I see Laurie and Jonathan had a conversation over the break about interpretation of benefit. We do concentrate on the risk side in our discussions, but obviously the benefit side is also important, where we are talking about the probability and magnitude of benefit parallel to the probability and magnitude of harm or discomfort.

So let's have a few comments about that since I think their discussion, as I understood it, was potentially instructive, potentially beneficial to our group. Laurie or Jonathan?

MS. FLYNN: Well, the comment that I made was, I continue to have real reservations about the structure that was laid out here in terms of greater than minimal risk with no potential benefit, in part, because my understanding of the concept of potential benefit is pretty direct, pretty immediate, and pretty readily and likely to happen for the individual who is the subject of research. That's what I thought our text was saying and that's my understanding of

potential direct therapeutic benefit.

Jonathan, I think, has a view that is different and appears to feel that the definition may be somewhat more elastic and more broadly applied in the real world than the way I'm seeing it.

I think it's useful for us to understand, how is that term defined, what is meant by potential benefit to the patient? I think we really had no conversation, no inputs from the research community or others, as to how that term of art is used when IRBs make decisions.

CHAIR CHILDRESS: Okay.

DR. MORENO: Laurie has expressed, in essence, what I said to her during the break. Namely that, without endorsing this view, my experience as an IRB member is that the notion of potentiality is, indeed, quite elastic and that investigators are given a relatively large amount of leeway in identifying what could conceivably be of benefit to the subject, including even simply a closer monitoring of the subject.

In the experience with the early HIV studies, for example, this was a very common point that was made

by investigators, that potentiality of benefit for subjects could include simply getting better health care. That gives rise to other issues about access to health care and so forth, but we're putting those aside for a moment.

So what I was saying to Laurie was that, perhaps in practice, more kinds of studies can be captured by the concept of potential benefit than one might at first think or one might think is philosophically ideal.

CHAIR CHILDRESS: Jonathan, since I don't have the document fully memorized at this point, I can't remember how well we do it in the document.

DR. MORENO: Probably not as well as we ought to do, because the document does try to walk the straight and narrow philosophical line that potential benefit ought to be -- a relatively compelling case ought to be made for potential benefit for the subject. But what I was saying was that, in practice, the way this washes out in the real world is that there is more breadth given to the concept than is done in the textbooks.

CHAIR CHILDRESS: Could you take as a task to

elaborate in appropriate places on that and we'll have further discussion on it.

Other points to be made? Let me, before we -- two other things should be mentioned about minimal risk. One, is the FDA has a statement on minimal risk and that sheet will be provided and circulated. So it will be sent to the NBAC office and then will be circulated to us.

Then, second, but we won't pick this up until Alex comes back in, there's also a research project under way at NBAC in looking at the literature of trials involving decision impaired subjects to determine, here again with the uncertainties about definition, those that involve more than minimal risk, and then with an effort to look at some of the consent forms related to those research projects. So we'll want to say more about that, and both those points are connected with minimal risk.

DR. CASSELL: On the issue of benefits yesterday when we were having that argument back and forth, there is a benefit to people to be treated as though they were normal persons, to be allowed to do what normal persons do. To be altruistic. One of the

things that normal persons do is to be altruistic, and that that is a benefit.

However, I do not want you to think that I think that's a benefit under the terms usually meant by benefit versus risk. The benefits we mean are direct, usually therapeutic benefits, not the benefits of belonging to humankind.

DR. MORENO: No. But what we're -- and what concerned Laurie was not the notion of directness, but the notion of potentiality. That is the issue that was of great concern to Laurie, and how the likelihood of benefits that might accrue to being in a study -- if there's 100 percent likelihood of feeling altruistic, I suppose, though I agree with you, that's not what I would, as a professor of medical ethics, consider to be a direct benefit of being in a study.

What Laurie was concerned about was the likelihood that this diagnostic test or this therapeutic intervention that was being examined would be of direct benefit to me as a subject.

CHAIR CHILDRESS: I thought it went beyond that, that this might well produce something that would be of benefit to me as a subject and not simply limited

to -- if we go the direction you're going in, Jonathan, it seems to me then that brings it much more clearly under what we would ordinarily think about using as traditional language, that we've gone beyond the therapeutic trials.

But I would take it that Laurie is looking at the review that, even in what we tend to think about as non-therapeutic trials, a possibility of developing something that would be beneficial should be included on the benefits side. Laurie, am I misunderstanding?

DR. MORENO: That's an accurate description of her thinking, just to be clear. What I was saying was that in the real world my experience is that much of what you and I sitting around an academic seminar table might think of as non-therapeutic is often construed as having benefit, not just the psychological benefits, but being observed by good doctors and nurses as part of the study might accrue to your well-being -- your medical well-being.

MS. FLYNN: Again, I was focusing on many of the kinds of basic neuroscience studies that are not intended or designed to provide immediate therapeutic benefit that are looking at the underlying etiology and

process of disorder. There's no immediate likelihood that my clinical condition, if I am a subject, is going to be enhanced. So I would agree with all of these discussions through the very narrow definition of benefit.

DR. MORENO: By the way, also in the real world I'm sure you've all seen on consent forms -- often one sees a consent form as a statement. One of the benefits to you for being in this study is being more closely monitored, having your condition more closely monitored. Many people would consider that to be a potential benefit.

CHAIR CHILDRESS: As we approach this and think about the revision of the document, one has to worry about excessive elasticity at this point.

Diane, then Trish.

DR. DUMAS: But knowing about that elasticity just increases my resolve that people for whom the risk is conceived to be greater than minimal should not be included in research projects. There's another point here, too. That is --

DR. MORENO: Just to be clear, you mean, should not be included in research projects without

their consent or --

DR. DUMAS: Without their consent.

DR. MORENO: -- without some analogous process.

DR. DUMAS: Without their consent.

DR. MORENO: Would you permit legally authorized representatives to make --

DR. DUMAS: Yes. There would be exceptions. Yes, of course. But I think a general rule --

DR. MORENO: Because that's the framework right now.

DR. DUMAS: The general rule is that people should be informed about the research. We should make every effort to make sure that they understand what they're consenting to in that process. Now, if there is some reason why that can't be obtained through the regular process, then the conditions under which there would be exceptions should be defined.

But there is also a mention in the document about benefits accruing not only to that individual, but to the population. I don't know whether we want to deal with that or not. If the benefit is to the population for which the person belongs, are we

interpreting that to be a benefit to the individual? I think that distinction needs to be made.

DR. MORENO: I think we're quite clear that that is not considered to be a benefit to the individual.

DR. DUMAS: As long as we're talking about potential or likelihood, I'm comfortable. I don't think we can promise anything more.

CHAIR CHILDRESS: Diane, then Trish.

DR. SCOTT-JONES: I was just trying to look in the draft, Jonathan, to look back and review where you talked about benefit and what it means. I am just trying to see how far we're going to go with this notion of quantitative judgments because we're sort of suggesting somehow that you balance the benefits against the risk and that you have some favorable ratio of benefits to risks.

I don't know if we want to do more in that regard than we've already done, and I'm not sure that that was the point of the comment that maybe there are more benefits than we've acknowledged in most research projects.

Is that the point, so that somehow the

benefits side will have more points on it in relation to the risk side; is that the thrust of the comments?

CHAIR CHILDRESS: Well, first of all, we've just not looked at the benefits side. If we're going to include the benefit/risk ratio in the determination we at least need to say something about it.

But, second, there was also a question about --

DR. SCOTT-JONES: There's quite a lot of it.

CHAIR CHILDRESS: That is in our discussion.

DR. DUMAS: Oh. Okay.

CHAIR CHILDRESS: Our discussion is focused only on the risk part. Then there's the question about whether it can be defined narrowly or broadly.

But I think -- either risk or benefit, it can't be purely quantitative because there is the qualitative element that enters in in even defining something as a harm or discomfort, et cetera. So it's going to be much more complicated, even if there is a quantitative sign.

CHAIR CHILDRESS: Trish, then Rhetaugh. I'm sorry. Diane, first. Sorry.

DR. SCOTT-JONES: I was just going to say,

here is already at least acknowledgement of persons saying that there are indirect benefits, such as diversion from routine, the opportunity to meet with other people, to feel useful and helpful, greater access provided to professional care and support. I think we've done a lot already to acknowledge these.

CHAIR CHILDRESS: Well, the point was, not in our discussion.

DR. SCOTT-JONES: Oh. Okay.

CHAIR CHILDRESS: Our discussion here. What we need to do is identify, since we don't have a lot of time, areas that we want to go back and now look at the report and make sure that the report does what we want it to do, and then Alex and Eric can just come in.

Then really take a Dali-like approach to this, namely, over and through e-mail and faxes over the next several weeks, really push forward areas where we want to make the kind of revisions so that we can come up with a draft that we can really go through very carefully and see whether that reflects what we, as a subcommittee and as a Commission, want to hold.

I have Trish, and then Rhetaugh.

PROFESSOR BACKLAR: I want to back up -- very

important when we go to this. We know there's potential benefits, just as we know there's risk of harm. There is that balance going on there. I also want to reiterate the subjective aspects of these personal benefits are hard to quantify. The other thing which I really actually believe we have in the report, that some of these benefits which Laurie is alluding to come about because the actual care for many of these people is inadequate.

Some people come into these protocols in order to get something they just don't get outside, just like people do who have AIDS. There are all kinds of research protocols going on with different diseases where this occurs.

CHAIR CHILDRESS: We'll take Rhetaugh's comment, then we'll turn to the issue I raised about the research project on minimal risk research that the NBAC staff is conducting.

DR. DUMAS: What I'd like to do is share with the group what I've said to some individuals, and that is that we need to give greater attention to issues of the characteristics or the constellation of IRBs because you can't quantify the factors that are

important to consider.

Ultimately, the people who sit on the IRBs will have to make judgments. We need to think very carefully about, as best we can, how those boards should be constellated to get the kind of judgments that we believe that they need to make.

CHAIR CHILDRESS: Alex, if you'll make your comment, we want to then talk about the research.

MR. CAPRON: Yes. I want to follow up directly on what Rhetaugh just said, because I was just having a conversation with Gary Ellis and I think it would be useful for Jonathan to take a look at the language about the special composition IRBs when they're dealing with research having to do with prisoners because, as Rhetaugh has emphasized, particularly when we're dealing with these vague standards, membership is going to be important.

Without having to get into the whole subject of how adequate IRBs overall are and what their composition is and their education, certainly an emphasis on a membership that would have a representative of the relevant patient populations that would be perhaps more heavily balanced towards lay

people and outsiders rather than fellow researchers and physicians, or physician researchers -- for this, would be a way of giving us some comfort that the process beyond the consent issue, which is so difficult for us, is adequate to the particular needs of this population where we have a history.

I want to just put on the table something. After our last meeting, I was sent a consent form for one of the studies of people who testified. I thought the testimony had been very interesting in emphasizing the quality of the consent process, and so forth.

The consent form didn't come up to that standard. I wrote the investigator asking for some clarification because I was afraid I was misunderstanding what was represented in the form.

The staff is now engaged in the project of looking at studies in this area that seek to involve more than minimal risk and where there are questions about the subjects being exposed to risk without real consent, and so forth.

We'll be following up to try to get some more consent forms to see whether they could usefully address that aspect of the issue, because I agree with

what many people have said about the importance of consent here.

We all recognize that the consent form is not equivalent to the consent, but certainly a consent form which itself has problems is not likely to be well remedied by aspects of many undefined -- about that. I mean, that's what the UCLA people said. Well, yes, the form was no good, but we had a conversation in which all this came out.

I think that the concern about the membership of the IRB is one way of addressing that because I think the more disinterested IRB would have looked at the form that I saw and said, wait a second, what does this mean, why are we saying this, is this accurate, is this conveying what's really at issue here? So perhaps we can address it and perhaps you could get some ideas from other areas of the regulations that already specify special make-up.

DR. MORENO: Could I just -- I want to make sure that I have good guidance right now from committee members. Alex, are you suggesting that I should draft further recommendations to the effect that not only the discretionary authority that the IRB now has to add

consultants and other members for specific studies involving vulnerable or special populations, but that those ought to be required for certain kinds of studies?

MR. CAPRON: Yes.

DR. MORENO: Okay. I just want to predict that people will raise questions about the impact of that requirement on the capacity of institutions to do studies with these populations. I can hear some folks whispering in my ear, perhaps not in this room, that the analogy to prison studies would constitute a significant drag on the ability to do research with these populations. Now, as a draftsperson I'm only pointing this out to you. I'm trying to anticipate an issue that this will --

MR. CAPRON: All protections of human subjects are a drag on the ability to do research.

DR. MORENO: Yes. But when we're talking about prison research we're talking about a relatively high threshold, as you know better than I. That is, again, something that this body needs to consider. I'd be happy to draft the language --

MR. CAPRON: Why don't you draft something and

we'll consider it when we have a draft.

DR. MORENO: Okay.

MS. FLYNN: Let me just ask a question, because I feel very strongly about this. And I appreciate very much your comments, Rhetaugh and Alex.

My organization several years ago drafted a policy that specifically requests guidance to IRBs who do review a great deal of psychiatric research, that they have as members of the IRB no fewer than two representatives of the subject population and that IRBs who do not routinely review this research have an affirmative obligation to bring on as consultants not only experts who are physicians and researchers, but those who represent the community who are the subject population. I guess I'm not clear what the burden is.

DR. MORENO: That language that you just used doesn't vary greatly at all from what is currently at the discretion of the IRB. What I heard Alex suggesting was that something along these lines, some proportion of the IRB, not only membership, but a further question is, should they actually be present for the discussion of that study. Very often these folks, as we all know, don't show up.

By these folks, I mean, community members have a hard time attending, very often. So it's not only a matter of having them as members on a piece of paper, but also having them actually sign off on the study.

MS. FLYNN: Yes. Yes. Yes. Absolutely.

DR. MORENO: Okay. That helps me.

DR. DUMAS: I feel very strongly that our best bet for getting change is through the IRB. If people in our communities don't show up at IRBs, we need to understand why. In some communities they do and they are very active. It's not comfortable for the scientists.

Most often, the groups have more scientists than other members. So if you've got one community member and they feel overwhelmed at not having a voice, I can see why they don't come. But we need to change that.

Well, I don't think I need to say anything more about that because the assumption in the past has been that the IRB is a scientific evaluative committee so it should be comprised of people who are involved in research and who have a commitment to the development of science.

I think that that is only partially true, that it should also include people who have some interest in the general welfare of those who are being involved in this process.

CHAIR CHILDRESS: Okay. Let me Eric to come in. Alex has to leave shortly, right? Would you like to comment on the research project?

MR. MESLIN: Sure. I'll just be brief about this and tell you where we are. A couple of stand-back are with us now and we can benefit from any input that the commissioners have.

Following the last meeting when Alex had expressed some interest in staff pursuing this we engaged in a number of search strategies, inductive search strategies, designed to identify those projects published in the peer review literature that seemed to meet this generalized concern of studies that involved greater than minimal risk for which not only the consent form or consent process might be an interesting indicator of whether or not protection was adequate, but also more substantively whether or not the research design itself raised any particular ethical questions.

So what we are now in the process of doing--

and it's a very intermediate process, there's nothing to present to you today--is we've identified probably several hundred abstracts that seem to meet this general threshold of concern.

We would love to hear maybe a bit more comment from commissioners as to what they would really like to see, because the next step in this process is to contact the investigators, identified obviously by authorship on the papers, and ask whether they wouldn't be prepared to share with us a copy of both protocol and consent form. This will serve a couple of, I think, very useful purposes.

One, since this isn't an investigation into unethical practices but merely an effort to understand what the nature of this research activity is, it would, I think, meet our public obligation at the very least, but it would meet, I think, the more substantive obligation to understand just what is going on.

Now, we realize that the publication of a study is not identical with our ability to understand all of the nuances of what goes on in the preparation of a protocol and how consent forms in the process might be carried out.

At this point, that is what our strategy is and we would hope to be able to complete a summative, if not formative, analysis of that within the next few weeks.

CHAIR CHILDRESS: Any comments on that?

(No response)

CHAIR CHILDRESS: One other thing, before Alex leaves, I'd love for us to decide, and that is whether we want to meet in February.

MR. CAPRON: Well, I'm not clear from yesterday's discussion we didn't come away with the impression that, if we're dealing with a topic in Los Angeles the next meeting, we ought to all be dealing with that.

So if the Tissues Report is in a position where it ought to be discussed, I would hope we don't have Tissues or Genetic Subcommittee meetings in which the rest of us would then come in and be presented again with something which would require, for Genetic Subcommittee people, to go over that ground again and either feel frustrated that we're all so naive and unsophisticated or that they've gone off in a direction which others are not happy with.

Likewise, I would hope we don't go much further on this report. We had some good feedback from the other commissioners yesterday and it helped to make clear for us areas where the report needs to be worked on. But from now on in, aren't we thinking that we're going to be meeting as a committee of the Commission instead as of a couple of subcommittees?

If so, Eric, Jim, I mean, it's really a matter of saying, how much are we going to have from our various work products that are ready for further discussion to be mailed out two weeks from now, which is really what you're talking about if you're going to have a useful discussion.

So part of the agenda may be this report and part of the agenda may be the Tissues Report, and the Federal Agencies Report, and whatever.

CHAIR CHILDRESS: I'm quite open on this. I understood from the discussion that evolved that the Genetics Subcommittee felt the need to meet in February to move their report.

MR. CAPRON: I'm just saying, we shouldn't let them meet by themselves.

PROFESSOR BACKLAR: Right. I second that.

MR. MESLIN: Sounds like we're going to L.A. in February. You will be hounded for your calendar availability, since we are currently trying to secure two dates in February. The two dates being either February 5, 6 or 6, 7, and not everyone has responded to that yet.

It would be very helpful, since the Genetics Subcommittee knows what it will be able to get accomplished within the next couple of weeks, i.e., within the next two weeks so that documents can be circulated in more than sufficient time for all commissioners to receive and think about them, it is not an entirely revised Stored Tissue Report, it is some specific aspects of that report that will be required for a focused discussion.

It would be very helpful if this subcommittee could also make the same kind of request of staff, or of Jonathan with us, for what it specifically wants to have on the agenda for the February meeting.

CHAIR CHILDRESS: Could I throw out some possibilities?

MR. MESLIN: Please.

CHAIR CHILDRESS: One, is we've had some

things identified that we need to work through. Some of those having to do with minimal risk and benefit, for instance, can be -- the addition of -- materials that we've not talked about.

Basically I would say our discussion with the whole Commission did not talk about the report. We only focused on a couple of recommendations. So I'm not at all concerned about not having something to do. I think we could have a very profitable discussion with the whole Commission about this report.

That, at least, is my sense. I don't know what others feel. We should really go through it and think it through, with the changes that will be made also. But not that we have to have made every single change we think would be important at this point.

DR. CASSELL: And in these two weeks we'll be doing back and forth. The two weeks before our document has to be produced we'll be going back and forth on e-mail.

CHAIR CHILDRESS: I should hope so, if people are willing to commit to that. I think we could have a document that would be just a step or two short. But we have to obviously get the whole Commission's

agreement on certain kinds of things, and some of that will come in February.

DR. MORENO: I just need to be clear, Jim, on what we can do and what I can humanly do in the next two weeks. Is your theory that the whole Commission will be working from the current draft?

CHAIR CHILDRESS: The current draft as modified, which would include any material -- any changes we can make in the discussion of minimal risk, et cetera -- the recommendations based on the discussion yesterday and today, doing the kinds of -- making the kinds of changes that we're committing ourselves to working on over the next several days and exchanging on e-mail.

DR. MORENO: I can certainly make some headway in modifying the current draft. I am a little concerned, though, that there will be confusion if I make -- some of the modifications are substantive, quite substantive, and that the full committee will then be at a disadvantage in not being able to keep straight which is --

MR. CAPRON: Do a cover memo. Just do a --

DR. MORENO: Yes. What I've done, and so

forth.

MR. CAPRON: Read these pages for that, and this is new material and very -- and we're all -- discussing it for the first time.

DR. SCOTT-JONES: Could I add to that that Jonathan already did some of that by noting points, like on page 143 and 144, issues we would need to discuss, things that are not in the draft.

I think doing that type of thing, and also bolding the additions so we would know the things that had already been done in response to previous concerns. I think all those kinds of things helped us to be able to --

CHAIR CHILDRESS: I agree. And we are going to have to have a discussion with the whole Commission on this document. I should note that the outside critics have had less to say about--and internal critics--about the first several chapters. It's really only at the end where most of the problems have come, but we need to think about how all the things integrate. So I think we really need to have that study -- having that with these modifications in February, if that would be suitable for --

PROFESSOR BACKLAR: I think the Genetics Committee is going to be very interested and very involved in the discussion -- same issues.

DR. SCOTT-JONES: I think, in addition to the cover memo, Jonathan, or I guess any one of us, perhaps you, Jim, could lay out for the whole Commission what these issues are -- in addition to their having them pointed out in the actual draft, because I think the discussion might be more productive now if it's really focused and not so wide-ranging.

CHAIR CHILDRESS: I agree. Jonathan, Eric and I will take the lead on that, but we'll circulate materials to you to review, that is, what we are going to propose along these lines.

DR. CASSELL: Just for clarification -- not making any changes in the hard copy before -- e-mail --

CHAIR CHILDRESS: We need to set a closing date for this. Let's look at the calendar and see exactly when NBAC needs to send out --

MR. MESLIN: May I make a suggestion, at the risk of helping Jonathan organize his work schedule. You all have his draft from today. I don't know whether everyone has given Jonathan any comments,

written or otherwise, based on that text. If you are intending to do so, please do that as soon as possible.

If you are also going to be providing additional materials based on the sort of homework assignments that seem to be coming out, please do that within the next week, i.e., within seven days.

DR. CASSELL: We are using as our baseline draft of December 22, 1997.

MR. MESLIN: Correct.

DR. CASSELL: Unchanged, at least until that week is past.

MR. MESLIN: Correct. It would be staff's hope --

DR. CASSELL: The baseline draft is this draft until seven more days.

MR. MESLIN: Yes. Right. And it would be staff's hope that two weeks prior to the full Commission meeting, or sometime in the week of -- I'm just guessing here --

DR. CASSELL: The 19th. I believe the 19th.

MR. MESLIN: Thank you. The 19th of January. We will be sending out the briefing books or have the briefing books being prepared with these revised

materials, giving the full Commission at least, and hopefully, two weeks with directions for how to make their way through the materials, cover memos, et cetera, for what needs to be focused on.

I mean, I'm pleased to say that with some of our additional staffing now that's something that we can do much more efficiently, and that you will come to the Los Angeles meeting prepared to discuss those items identified in that cover memo. The full Commission will receive all materials from this point forward.

Is that what seems reasonable?

CHAIR CHILDRESS: Any dissent to that?

(No response)

MR. MESLIN: This is a good time to talk about the dates.

CHAIR CHILDRESS: Okay.

MS. HYATT-KNORR: The only other issue I would like to raise is a very simple one, namely, which date would you like to pick. The 5th and 6th would be Thursday/Friday, the 6th and 7th would be Friday/Saturday. We have all agreed on the 6th already, the question is just, which day would you like to add at one end or the other for yourselves.

DR. CASSELL: Would we have to start first thing in the morning on Thursday if we started on the 5th?

CHAIR CHILDRESS: Could we start early afternoon? I think that would be helpful for --

DR. CASSELL: We can travel out. You want to use the Thursday to get out there anyway. It's just a question of getting an earlier flight.

DR. SCOTT-JONES: I can't. I'd have to do it Friday and Saturday. I teach on Thursday.

CHAIR CHILDRESS: Friday and Saturday.

MS. HYATT-KNORR: Thursday and Friday.

PROFESSOR BACKLAR: It doesn't matter to me either way.

DR. CASSELL: Thursday/Friday.

MR. MESLIN: What we will likely have to do, is we will have to take one final poll with the rest of the Genetics Subcommittee members as well, and we'll have to make a decision that allows everyone to obviously be there on the 6th, which will end up being a full day. Some will be able to come for the half day, which may turn out to be the way we do this, either on the 5th or on the 7th.

So I hope you will appreciate that as we're moving into this new arrangement towards full Commission meetings with everyone participating, that every effort will be made to attend as much of the meeting as possible.

We realize that this is difficult, and we're making these dates on the fly with previously existing commitments for your day jobs already in place. Hopefully by February forward, we will be able to schedule the rest of the Commission meetings along the lines that we had discussed in the planning bucket yesterday. So no one should take it personally if your preferred dates are not the dates that the Commission will be meeting in Los Angeles.

CHAIR CHILDRESS: But it sounds as though everyone can make the date that had been previously scheduled, and that's very important. Okay.

Any other discussion of what we need to do on the report, because it's almost 11:00.

(No response)

CHAIR CHILDRESS: We do have two people who have indicated that they would like to offer public testimony. If anyone else is interested in doing so,

if you would indicate to a member of the staff.

Jack Schwartz and Bill Freeman, could you wait until after the public testimony? We only have two people who are planning to testify, we can go ahead and do that since we planned to do that at 11:00, if that will be all right. Okay.

First, is there anything else we need to say about how we're going to proceed on the draft report? I think we may have covered everything we need to. But let's plan to be active and revive the e-mail exchange program and move very quickly on this. All right.

I know some are having to leave, Alex in particular. Let me just thank everyone at this point for being here and for a productive day and a half.

The first person presenting in public testimony is Mr. John Cavanaugh-O'Keeffe, who needs no further introduction. He is with the American Bioethics Advisory Committee.

And you know there's a five-minute rule, I'm sure.

STATEMENTS BY THE PUBLIC

Statement by: Dr. John Cavanaugh-O'Keeffe

American Bioethics Advisory Committee

DR. CAVANAUGH-O'KEEFE: Got it. Yes. Thank you very much, Doctor. I wanted to issue an invitation, with a quick preamble.

I was very much intrigued by Dr. Rhetaugh Dumas' question yesterday, or challenge to the Commission, why is it that it's so difficult? What are the underlying issues? As we look at protection of human subjects, is there something that's not on the table?

Why is it that this, which appears to be simple, in fact, becomes radically complicated very quickly? It did seem to me that at least one of the underlying issues is the issue that Ms. Kramer mentioned this morning, and that's the question of trust or lack of trust.

What came to mind for me was the issue of spina bifida research. During the second World War, spina bifida nearly disappeared in Great Britain, but for the next 50 years researchers looked for the genetic predisposition for it.

Almost all, 99 percent of research on spina bifida from World War II until about two years ago, was a complete, total waste of time. Nearly everybody who was born with spina bifida, or 90 percent, after World War II need not have been born with that condition.

If anybody had looked at what happened 50

years ago, what they would have found is that it can't be a genetic predisposition if it disappeared during a war.

What happened in Britain? It was only fairly recently that people looked at that and realized that, during the war, the British were on rationing and were eating government-made bread which had Vitamin A added. That need not have waited 50 years.

I think that it is fair for people to be extremely angry at a research establishment which, for 50 years, ignored a cure that was staring them in the face. So I think that the question of trust is the underlying issue that Dr. Dumas was looking for.

Responding in a tiny way to that, I wanted to issue an invitation. That is that on January 23 there is a Pro-Life college group from the midwest that will be sponsoring a protest in front of the offices of the National Bioethics Advisory Commission dealing with the issue of human cloning.

They've invited me to come speak there, and I said that I would. But I would also really urge that anybody from the Commission who would like to come out and talk with these folks, I'd really urge you to come

out and do so. I think that they would make room for you on the program, if you wished to do that.

But whether you want to speak or just listen, I'd really urge you to respond in some kind of way.

Doctor, thank you very much.

CHAIR CHILDRESS: Are there any questions, comments?

(No response)

CHAIR CHILDRESS: Just a question for clarification. The focus of the protest would be the report or --

DR. CAVANAUGH-O'KEEFE: The issue of human cloning, responding, I think, to the NBAC's Human Cloning Report.

CHAIR CHILDRESS: And you say that's going to be held --

DR. CAVANAUGH-O'KEEFE: That will be January 23. It's in conjunction with the Rowe v. Wade protest of January 22. This will be the next day.

CHAIR CHILDRESS: Any questions on this?

(No response)

CHAIR CHILDRESS: All right. Thank you very much.

And Dr. David Shore of the National Institute of Mental Health.

STATEMENTS BY THE PUBLIC

Statement of: Dr. David Shore

National Institute of Mental Health

DR. SHORE: Good morning. I'm here representing the NIMH, taking the place of Rex Calgary, who has moved on to try and serve as a liaison between the clinical research community and the private sector, perhaps moving from a difficult job to an impossible one. We shall see.

I just wanted to make four brief comments, and I'll try to stay within the five minutes. First of all, I wanted to let you know that the intramural research program at NIMH has finished their investigation of some of the allegations that were presented to this group previously and that we have, as you call it, a penultimate draft that we have delivered to Dr. Childress conveying a number of action items. If there are questions about those as you look at them, please let us know and we will try and clarify any of those issues.

The second point I wanted to mention was that, as you heard, December 2nd and 3rd of this year we did

have a trans-NIH panel meet to discuss some of these same clinically relevant issues in research involving those with questionable capacity, uncertain capacity. We've certainly gone back and forth on the title several times as well.

This panel report is in draft at present. It is circulating to members of the NIH community and should go out to members of the panel this coming week. We would hope to have it available for you by the end of this month.

I can tell you that it will focus on guidance for IRBs, the idea that there are already provisions in Federal regulations that permit additional safeguards for certain populations in situations in which there might be increased risk, and we are going to try to make some clear recommendations as to how IRBs might best take advantage of those additional safeguards.

So if I can just say that perhaps we're not so much anti-legislation or anti-new regulation as we would like to take advantage of some of the safeguards and protections that currently exist and may be perhaps under-appreciated by some of the local IRBs.

The third point, is that we did have some

concerns with the November 1997 draft. We greatly appreciate your sharing that document with us and allowing our staff to take a look and make comments.

You all now have copies of the critiques of some NIMH staff about that and, in particular, our concerns that the very scholarly imbalanced text be reflected in the specific recommendations.

Unfortunately, these days generally executive summaries and recommendations are read at the expense of thoughtful and deliberative text.

Finally, I just want to echo the concerns of some of the members of the Commission, that you continue to get input from experts on clinical research, in particular involving those who have done research involving individuals with psychiatric or neurological impairments to inform the NBAC about some of the clinical disorders and some of the nuances of clinical research.

CHAIR CHILDRESS: All right. Thank you.

Are there any questions or comments?

(No response)

CHAIR CHILDRESS: Let me just ask one, if I could. Incidentally, regarding the response to the

allegations, that will be sent to all Commission members by the NBAC office next week, or this week, I guess. Tomorrow. Today or tomorrow.

But regarding the other draft which members of the subcommittee, at least, had a chance to see, I guess one question was whether, since a misunderstanding came up in the meeting yesterday about whether what we were proposing in the recommendations would apply to more than minimal risk research or whether it was only to more than minimal risk research or also to minimal risk research, it seemed to me that the response from the National Institute of Mental Health actually thought that we were making this apply to minimal risk research too, so some of the things that would be excluded from your interpretation, actually, would not be from ours. I apologize, because there unclarities in the document on that point.

DR. SHORE: Right. At the end of the document that you drafted, and of course that's the November '97 version to which we had access, it did appear to, in effect, prohibit even minimal risk research on those with questionable capacity to consent in a case in which it was non-therapeutic or no direct benefit,

depending on which term you use.

We believe that there are certain circumstances in which greater than minimal risk research might be justified without direct benefit, but we are certainly willing to concede that in such situations additional safeguards should probably be employed.

I expect that we will advise IRBs as to additional steps, perhaps independent monitors, that might be used to assure that input from the family, from independent clinicians, et cetera, is used to best advantage.

But our major concern was that the version that we saw did not appear to make the distinction between even minimal risk research, asking a few questions of an individual or taking a tube of blood and would appear to outlaw such studies which have been so useful in finding the genetics of Alzheimer's disease, for instance.

CHAIR CHILDRESS: And that has been clarified. The revised draft that we're working with also incorporates the input of several subcommittee members who had the opportunity to attend the conference in

early December, a very beneficial conference. It was, indeed, for all of us.

I guess one question would be whether you'd mind if we go ahead and work with the draft of the recommendations that are coming out from that meeting because, as you've heard our schedule, we are trying to move forward, if you think it would be appropriate for us to go ahead and least use that for our reference at this point, would be helpful.

DR. SHORE: Perhaps we can compromise on what I may call our penultimate draft, and I can make a promise to try and get that to you, say, two weeks before you meet.

I don't feel completely comfortable, of course, in sharing with you a document that has not been vetted by the members of the panel, but, as you may know, I'm not the most patient individual myself so it is my desire to get this in final form as soon as possible and get it to you immediately thereafter for penultimate form.

CHAIR CHILDRESS: Anything else?

DR. BRITO: It would be helpful to have a specific example of what you mentioned, that there are

greater than minimal risk research has been useful in the past, something that's been done. So if we could have specific, concrete examples of that, that would be really helpful.

DR. SHORE: I mean, I would just say things like PET scans in suicidal adolescents, spinal taps.

DR. BRITO: But the references and the publication. Appreciate it.

CHAIR CHILDRESS: Thank you.

Does anyone else wish to offer public testimony?

(No response)

CHAIR CHILDRESS: All right.

Let me then turn to Jack Schwartz. Thank you, Jack, for bearing with us in the modification of the schedule. Jack will provide an update on the Maryland Attorney General's Working Group. You have seen several drafts from this working group over the last year, and we're glad to have Jack offer an update.

UPDATE ON MARYLAND ATTORNEY GENERAL'S WORKING GROUP

By Jack Schwartz, Esq.

MR. SCHWARTZ: Thank you. I'll summarize the current status and identify some current issues pending before our group. My summary of those issues will make it plain, I think, the areas in which we need your help.

The Maryland Working Group has been about its task for more than two years. Our objective was to

come up with a draft statute on research involving decisionally impaired people that could actually be enacted by the Maryland legislature.

That last qualification is an important one. I daresay that many members of the Maryland legislature have never even heard the word "bioethics" but they know a bioethics controversy when they see one and they know how to avoid it.

So for legislation of this kind to have a realistic chance of enactment, it must arrive at the legislature with a fair degree of consensus. If the hearing on the bill turns into an ethical debate, the bill will simply disappear without a trace.

A consensus is not achievable without something that resembles a public conversation. So we have been at pains to try to have public reaction to our thinking as we go along through the medium of now three reports that we issued soliciting public comments. The last two of these three included draft statutory language that people could react to. The more you ask people to give you comments, the more they do.

So a satisfying aspect of this process is

that, at least in the last go-round, some people participated, reacted, who didn't have an a priori interest in the subject, people who had no particular organizational identification, leaders of religious groups in Maryland, advocates for the homeless.

Their overall reaction was twofold. To think that the essentially unregulated status quo about research involving decisionally impaired subjects was unsatisfactory, but that the proposal then on the table, the August '97 version of our document, fell short in a number of respects. I'll summarize those in a moment.

But the upshot, from my perspective, is that, given the current reaction to our draft that's on the table, given the prospect that you all will serve as the cavalry coming over the hill to save us in some respects, that it was not ready for introduction in the session of the Maryland legislature that begins next week.

Hence, we will not offer a proposal in the '98 session of the legislature, which is a three-month session. Essentially, if we were going to do it we would have had to have done it by now. That is to say,

have a draft that was essentially ready, talk to key member of the legislature. None of that has happened because we're not ready yet.

So we will have the opportunity to be guided by the Commission's report as we continue this process. I anticipate that we'll have another draft out by middle of spring, again, soliciting public comment. Our goal method was to try and share our thinking as we went along. That's been fruitful, and I commend that strategy to you.

Let me try and summarize in general terms the reaction that commentors had to the proposal that's now on the table, our proposal.

The first, was to be nervous about something that we did not include in the document that we left out, and that is the issue of capacity assessment. The current Maryland draft simply takes as a premise that the individuals who are the potential research subjects are decisionally incapacitated and regulates from there.

Well, there was much focus on the lack of discussion or lack of provision in the bill for a process of capacity assessment, so we are wrangling

with that. Our sense, of course, is that despite the excellent scholarship in this field, Dr. Applebaum's and others', that there is no broad agreement within the field on the methodology for capacity assessment.

Hence, I think it is likely that our next proposal will simply impose an obligation on researchers where the research subjects have a condition that raises a red flag, if you will, about capacity to describe what method they are planning to use to assess capacity and charge the IRB with reviewing that recommendation or that proposal by the investigator.

Hence, there will be no command and control state regulation, but instead the obligation on the part of the investigator and IRB to address the issue.

The commentors were wary of things that we had included in the measure, not only things that we had left out. There was considerable concern over a topic that you all have addressed this morning, and that is Research Advance Directives and the circumstances under which those ought to be given the legal security of a statute.

An interesting aspect of concern was, what is

to prevent investigators from potentially turning these into blank checks, to essentially solicit the signing of a research advance directive upon admission to a facility, worry that if the provisions on advance directives were too open-ended, that it might invite abuse of that kind.

A second aspect of concern was over capacity, assessing capacity to executive an advance directive. There seemed to be general recognition of the truism that people may have differing capacities for differing decisions and, therefore, the fact that an individual might not be capable of giving informed consent to research participation did not necessarily imply that the individual lacked the capacity to execute an advance directive.

Those are different decisions, depending on what the advance directive is, of course. I'm speaking now of proxy-type advance directives designating a substitute or surrogate decision maker.

Yet, there were worries that at least the -- in situations where an investigator had determined that a potential research subject lacked the capacity to give informed consent and yet then solicited an advance

directive, was a worrisome phenomenon and, hence, ought to be addressed through some provision calling for, at least in those circumstances, an assessment of capacity to execute the advance directive, a separate issue than capacity to give informed consent.

There was worry over elements of our proposal that essentially borrowed Federal concepts. We had understood our own role from the outset as being unable to fix problems that arose from the common rule itself.

So, insofar as there are difficulties, as there plainly are, with the definition or concept of risk, as reflected in the Federal or in the common rule, we imported those difficulties into our proposal because we simply borrowed the definition of minimal risk and erected categories of risk based on that sandy foundation.

But we didn't think that we could, in Maryland, do anything useful by way of addressing a problem that is a fundamental one, as you've identified, and that has national import, and we have been criticized for that.

How can you, people say, invest substitute decision makers with authority in particular categories

of risk when, to borrow Professor Capron's phrase, the categories are bounded by pieces of spaghetti.

There isn't any satisfactory answer that we can give to that, except this was sort of the given for us. So to the extent that the Commission is able to help inform our understanding of risk and, hence, of the categories of decision making authority that can be built on risk, we would be most grateful.

Another issue that will engage us at our next meeting in, I think, early February has to do with what limitations, if any, state law ought to place on participation by decisionally impaired subjects in placebo-controlled studies.

The concern is over circumstances in which there is standard therapy and yet individuals with decisional incapacity are enrolled in placebo-controlled studies so that they are removed--one arm of the study--from their standard therapy and given placebo.

As usual, we lack data in knowing how often this occurs, but the commentors were worried that the proposal, as currently framed, would allow that because it really doesn't address very much about placebo, or

the control aspects of a randomized clinical trial. So that's another matter on our particular table.

So those are what we are grappling with. Any aid from you all would be deeply appreciated. We will be having a set of discussions within the working group over February and March.

I would imagine by late March, early April we ought to be in a position to again share our thinking with you and the public through the publication of another report.

The idea would be to be in a position by summer to have completed our work and identify consensus, if there is one, and then go about the business of trying to develop legislative support for the proposal.

CHAIR CHILDRESS: Thank you. Thank you very much, Jack.

Are there any questions or comments?

(No response)

CHAIR CHILDRESS: Well, thank you very much.

MR. SCHWARTZ: Thank you.

CHAIR CHILDRESS: We appreciate your sharing with us.

Bill Freeman. I saw him a moment ago. Oh, he's on the telephone now. The latest word, is that right, Bill?

DR. FREEMAN: Not quite.

CHAIR CHILDRESS: Bill, we're grateful to you for updating us on the report.

Let me just mention, for those who may not have been here when we talked before, the plan is to complete the report from the Genetics Subcommittee and the Commission as a whole on tissue samples and the one on decisionally impaired research subjects, and then to complete the one on the Federal Agency Report, perhaps in conjunction with recommendations about Federal oversight. So this will be the third report released. The data collection is still in process, but almost done. So Bill is going to update us about that.

UPDATE ON REPORT ON THE SURVEY OF FEDERAL AGENCIES

By: Bill Freeman, M.D.

DR. FREEMAN: Becoming the third report has given us room, time, to do more things that we need and want to do. We are greater than 90 percent at Phase I. That was a structural survey of every agency that has signed on, including some agencies that did not sign on that we found are doing research.

We're greater than 70 percent at Phase II. That's a smaller number, looking at a range of various kinds or sizes, et cetera, of IRBs in those agencies that have them or in the mechanisms for grants and contracts, what are the procedures to make sure that grants are contracts are -- on these institutions that have the protections in place. You've seen in the past

the general, broad conclusions. They remain.

We continue the process, and I want to emphasize this, that every agency has reviewed our draft--or at least has been given an opportunity to review our draft; we can't make them do it--for the facts at the time of the survey and gotten back to us.

They have that opportunity, and we will come to an agreement about what those facts are before the first draft about that agency gets to you. That review also includes any other modifications or suggestions they have.

So if, for instance, there was a rumor that some agencies thought, well, maybe they didn't present themselves, didn't take it seriously when they interviewed them. There's plenty of opportunity to set the record straight. This is an iterative process, really, as long as it takes, and also for additional suggestions.

Those suggestions, by the way, are coming in. We asked for those initially and I think it would be very helpful about how to implement the regulations.

One of the things that was suggested a couple of meetings ago has been modified a bit. We aim,

before the completion of the report, to have at one of the NBAC meetings -- invite Federal agency officials to come and talk about their suggestions about how to improve the implementation process of these regulations.

They will also, of course, be able to make generic statements about our generic suggestions. We will not, we hope, get into defending or attacking any given agency. That's not the purpose of our report, or the purpose of that meeting, for that matter.

Finally, staff have developed also over the holidays, given it was difficult to meet with people, possible general implications--and we're still in the process of this--for adoption or non-adoption of innovations by agencies. It's from the political science and sociologic literature. This may complement the papers by McCarthy, Fletcher and Gonzales about, they're primarily on location in the Federal Government for Federal oversight.

This would be more, what are the functions or the processes that should be included in this entity, whatever it is and wherever it is, to maximize the innovation -- the acceptance -- excuse me, the adoption

of these regulations that we have found have not been adopted 100 percent throughout the Federal Government.

Of course, you'll be getting plenty of a chance to look at that in a draft. But we have found some information that I think has turned out to be very, at least at our first glance, very helpful.

CHAIR CHILDRESS: Well, thanks very much, Bill, and other members of staff who have been working on this project over many months.

Are there any questions or comments for Bill?

(No response)

CHAIR CHILDRESS: Okay. Bill, thanks very much, again, and to the staff working on this.

I had got a note to ask Jonathan Moreno to say something about the TD case, and Jonathan came up to say that Jack Schwartz was the person to ask about the TD case.

Jack, if you wouldn't mind just telling us where matter stand as that has evolved.

MR. SCHWARTZ: Sure. Just a little recap on that. The TD case involved a challenge to the legality of regulations that had been issued by the Office of Mental Health in New York governing research

participation by decisionally incapacitated people in mental health research.

The original decision, the trial court decision, had invalidated the regulations on a rather narrow ground, namely that the regulations were not properly issued by the mental health office, but rather were within the authority of the New York Health Commissioner; not exactly a technicality, but a relatively narrow ground.

When the case came to the intermediate appellate court in New York, that court agreed about this who has the authority question, but then went on to suggest that there were significant constitutional problems with the regulations.

This intermediate appellate court decision suggested that there were constitutional reasons why individuals with decisional impairment could not be involved in non-beneficial research that posed greater than minimal risk, some extensive discussion in that opinion of constitutional and common law issues.

The matter was brought to the New York Court of Appeals, which is New York's highest court. In a decision about three or so weeks ago, that court in

essence vacated throughout the portions of the intermediate court decision that had dealt with the more interesting issues, the constitutional and common law issues.

So the state of the matter is that the only thing that this case now stands for, it's the incredible shrinking case. It now stands for the narrow proposition that it was one official rather than another in New York State that has the authority to do these regulations, and the discussion of constitutional issues is now tossed out.

So what happens next? The New York Health Commissioner presumably will do regulations. There's a task force at work in New York to provide advice to the health commissioner.

Once those regulations are newly issued, then presumably the plaintiffs in the case, if they are dissatisfied with the new regulations, can start their challenge over again, again alleging the constitutional problems that they perceived before. But we are years, presumably, away from an authoritative decision on that matter.

CHAIR CHILDRESS: Any questions about that?

(No response)

CHAIR CHILDRESS: Thanks very much.

DR. MORENO: And I'd just say, as a member of that -- task force, we're waiting to see what you guys have to say about this too, as are the good people in Maryland.

DR. CASSELL: There's a kind of circularity in the Maryland and New York task force and NBAC.

CHAIR CHILDRESS: And it all comes back to you, Jon.

We have scheduled a brief discussion of future Commission research activities. I wonder if Eric could lead us on that. We won't spend a lot of time on this, but notice the number of topics that were identified that have to do with research. So let's see if there's any feedback on that.

DR. CASSELL: I cannot be the only person who has a certain feeling of both dejà vu and frustration in this discussion as we go around and around on subjects that were impossible to solve the last time around, and here we are again. Only we have done one significant thing, there is no question about it. We have added a surrogate. We have added a friend. That

is no small matter.

On the other hand, it seems to me that one of the things we always end up on, is we come back to the IRB. We're going to let the IRB do this and the IRB do that. Yet we all know, almost everybody who for any length of time has served on IRBs, and some of us have even chaired them for prolonged periods and we know their difficulties, that IRB members have variable knowledge of what they are actually doing and we know that there is even in some cases questions of good faith in IRBs, depending on where they are, and so forth.

The point is, I cannot see how we can avoid the subject of research on IRBs toward -- toward a change in the IRB method. Now, having said that, I think it's a matter of discussion, what, in fact, does that mean. I think Eric already has some things going and we might have a discussion here, a brief discussion, to go home with.

Well, what does that all mean; what do we want to do as a Commission? If we leave this subject and don't do something to change this, I think we would have been remiss. We had a dinner meeting last night

that came to much the same conclusion.

Eric?

MR. MESLIN: Well, at the risk of belaboring the discussion, there was full Commission discussion on this subject yesterday. One of the decisions the group seemed to come to was that there was a general consensus that all of those topics were extremely interesting and relevant.

It might be useful if you were to pick up Dr. Cassell's challenge of identifying the top two or three that you thought were most urgently pressing, and I think Arturo mentioned this yesterday as well, that we can do and that we can do well.

Several of these have come up, including the IRB study, the study of international clinical trials. It may be useful for you just to ruminate once more about where you see the importance for the full Commission going forward, because we will revise this planning bucket document and recirculate it.

Harold's wish yesterday before leaving was that we would pick this up at the next meeting of the full Commission, so don't feel constrained by a decision to come to closure today.

DR. CASSELL: Then there's the other subject which is mentioned, and we have documents on, is it comes out of the paper on the capacity consent in neurobiological research, the Berg and Applebaum paper. My own direct investigative experience -- this paper is a sea of misunderstandings and poor definitions. The word judgment -- we're talking about people making a judgment.

What people mean by a "judgment" is not at all clear through this. Repeatedly, everybody's experience is that people given consent forms frequently do not understand the content of their consent form, never mind remember it.

That's already a different issue. But they do not understand the content of the consent form, medically ill as well as psychiatrically ill patients. Yet, we continue to do the same kind of thing as we did before.

So I don't really know what the answer is. I would hate to leave this meeting feeling, well, okay, what you have to do, is every Commission has to sing the song and dance the dance, then wait for the next Commission to have some bright idea about what to do to

solve it.

But I actually think if we start with where we are going and continue research into the nature of the thing called consent, that we will have made a contribution, if it clarifies how we believe people should give consent to research and what safeguards we have for that consent.

I have a side feeling that we are going to have to figure out what community means in this relationship and we haven't figured that out yet either. The fact that we haven't figured out all these things doesn't bother me in the slightest, if we pick them up. If we don't, then it's --

CHAIR CHILDRESS: And we do have a paper, a contract paper on community that will be circulated in the next few weeks after some minor revisions.

PROFESSOR BACKLAR: It's interesting that in the remarks on the November draft, that NIMH seemed very much at sea and misunderstood our references to community -- show that we --

CHAIR CHILDRESS: Bill?

DR. FREEMAN: I'm sorry. I didn't hear that well where I was. Is there a concern about people

being at sea about the community; was that the statement?

CHAIR CHILDRESS: That in the response from the National Institute of Mental Health to our November document, there were some expressions of concern about our invocation of community and how we were going to use that.

DR. FREEMAN: CDC -- not in the mental health field, as far as I know, but CDC has just come out with a not-very-thick book about the role of community in research, which is some of the best that I have seen, and includes the Mohawk of Tanawaga in Montreal and their involvement in research, and others.

I ought to be able to get copies for the entire Commission. There will be some perceptions from the point of view of community people and researchers who have worked with them about what that relationship can look like.

CHAIR CHILDRESS: Can you get that to us fairly quickly?

DR. FREEMAN: Hope to get it probably within a week.

CHAIR CHILDRESS: Good. That would be

helpful.

Bette?

MS. KRAMER: This is a question of process. I was wondering if it would be possible for the staff to do some research into the existence of some good material on issues like consent, such as what Bill refers to about community, because even in as a preliminary move we can make reference to those materials in our reports, and I think that that would be an addition.

MR. MESLIN: Are you asking about research that's been done and the concept of community consultation and whether it's been affected?

MS. KRAMER: Yes. But no consent.

MR. MESLIN: Consent as a broad --

MS. KRAMER: Consent forms. The process of consenting to research.

MR. MESLIN: We can certainly discuss that, sure. Let's do that outside.

MS. KRAMER: All right.

CHAIR CHILDRESS: Okay.

FUTURE COMMISSION RESEARCH ACTIVITIES

CHAIR CHILDRESS: Other points to be made about future research and Commission research activities. I guess one possibility would be whether we want to recommend, in terms of the list that Eric's committee provided, and that the Commission went through, whether we want to make any recommendations about priority.

I don't recall that we actually set any priorities. There are some things that have a kind of immediacy about them that you noted in your report and in your discussion. But are there any comments that you would like to make about that, since I assume that the Ad Hoc Committee may well be providing further

guidance.

DR. CASSELL: It was our hope that people would reflect on -- well, let me divide it up again. We had two categories. We had an immediate set of problems and we discussed those, then we had these larger issues, the limits of clinical medicine and ownership of body is two examples of them, that people have to sort of chew around and decide, is this a subject for us.

It's easy to see that the report acts as though this Commission will go on beyond its present allotted time, and it's like time will be extended because of what we've already discussed.

The immediate needs will carry us to 1999 without -- but it is our hope that people would pick up, particularly, Alta Charo's, what does it mean to say? I mean, we take it for granted that people are giving a consent to have something done to their body. That implies a certain kind of relationship to the body and -- spelled out what that relationship is. That would be an interesting subject.

Certainly we can't even come near reproductive technology, I would think, without beginning to

clarify, what is the woman's relationship to her body and to what it does, because those are issues that bear directly on reproductive technology.

The limits of clinical medicine issue is also -- it's a question that we keep coming up against here but we bounce back, and that's the question of progress. Is scientific progress an unlimited good? As Alex pointed out, quoting -- it's a limited good.

There are greater goods. I have a colleague at the head of the table once who reminded me that saving lives was not the highest good, that there were greater goods than that. I think freedom was one at the time. These are issues that I think we have to consider for the future to determine our work and set us on a course that commissions have not yet started.

CHAIR CHILDRESS: So this is viewed as a process then.

DR. CASSELL: Yes.

CHAIR CHILDRESS: The question is whether we have anything we want to suggest at this point, or simply, as Eric has noted, reflect on this, since the question of priorities would be addressed at subsequent Commission meetings.

Anything you'd like to add?

DR. BRITO: My general feeling, talking to different people in the Commission, is that the IRB problems -- I think almost everyone that I've talked to agrees that that's probably -- they agreed with your comments yesterday about that being a very important issue, and I think we should proceed with that -- start to proceed with that at some point in the future.

The only problem with that, that's such a big topic that it will take time. In the meantime, that could be our big topic to cover. We could refer to the more focused topics and pick a few to also do in between.

CHAIR CHILDRESS: -- it seems to me that we should have at the February meeting an update from the two groups currently studying IRBs and begin to plot with staff sort of what's the better move and what might be done. So I think that's an important thing we could recommend to the Commission as a whole, depending on what comes in.

DR. BRITO: And the topic of limitations of clinical medicine, et cetera, even though it's something I'm very interested in, I'm not sure how much

that deviates from what our goal is to protect substantive research. I don't know. I'm just tossing that out.

DR. CASSELL: I think everybody should recognize that us education freaks on this Commission know that issues of IRB bring up issues of education and issues of investigator information, and so forth. So for all of us, these are sneaky ways of bringing in the --

(Laughter)

CHAIR CHILDRESS: Diane?

DR. SCOTT-JONES: I would just like to follow that with a comment that I've been reflecting a lot of the references to the IRB today and yesterday, and even though I agree with the general sentiment that there are lots of problems with the IRBs, I think that we can't really consider IRBs without also considering the regulations with which they have to work, the guidance that they're given, which also are problematic.

Then on the other end, the researchers who want to move forward their research without delay, who also make demands on the IRB, so in some ways IRBs may be caught in the middle without appropriate guidance,

without clearly defined regulations, and then on the other hand being perceived as obstructionist by persons who want their research to move forward without any delays. So I think we need to look at both of those ends at the same time.

DR. CASSELL: Let me make it clear, I agree with you entirely in that I would say that it isn't IRBs, per se, it's the process of institutional review. It's the process of institutional review which adds -- investigators in the institution with pressures on the --

MR. MESLIN: Since it appears that in the report yesterday, which was divided into two components, a set of procedural issues and a set of substantive programmatic issues, has at least been 50 percent dealt with. Many of the process issues were addressed yesterday by the full Commission and I think agreed to to a substantial extent.

Would it be helpful to the commissioners if, before the full Commission meeting in February, staff would prepare a brief memo summarizing these items in the program and listing, if you will, what the kinds of research projects might arise from those, if you will,

topical areas?

We could go so far as to offer a provisional priority for you to respond to, or it could simply be in a non-lexical order and give it to you alphabetically.

But now that you've dealt with many of the process issues, we'd be pleased to provide that list of the sort of seven, eight, or nine items, with a brief descriptor of what we think you might mean by those topics.

DR. CASSELL: I would find that enormously helpful.

CHAIR CHILDRESS: Good. I agree.

Trish?

PROFESSOR BACKLAR: Maybe I missed this, but -- if you would need to talk about putting this report --

CHAIR CHILDRESS: Well, my assumption, at least -- I can't remember what we said about it. But my assumption was that we wouldn't do that before the next draft.

PROFESSOR BACKLAR: Well, I wasn't thinking that.

CHAIR CHILDRESS: Yes. But I think the -- agreement to do that. Is that right?

DR. BRITO: That's what I thought.

CHAIR CHILDRESS: I agree.

DR. BRITO: I forget when the conversation takes place sometimes, but we're almost ready -- or 60 days before --

PROFESSOR BACKLAR: I was talking about -- what you suggested -- report.

DR. BRITO: For the Web site.

CHAIR CHILDRESS: Yes. Maybe I'm wrong, but if there's no objection, I thought we had come to an agreement on that.

PROFESSOR BACKLAR: Yes. I'm sorry. Yes.

CHAIR CHILDRESS: But if there are any objections to that, I think --

Anything else you would like to raise, Bette?

MS. KRAMER: Jim, to return to the prior subject, there was one issue that was mentioned some time ago that wasn't captured in the list that Eric presented yesterday. That was the use of genetic tests -- making genetic tests available to the public, in fact, encouraging the public to make use of genetic

tests before there is an approved therapy.

CHAIR CHILDRESS: Eric, was that considered as a --

DR. CASSELL: I didn't hear that. I'm sorry.

CHAIR CHILDRESS: Could you repeat that?

MS. KRAMER: I mentioned to you last night the use of genetic tests before there's an approved therapy.

DR. CASSELL: That was not brought up, but certainly you can raise it now. As I said last night when we discussed that, there was quite a lot of literature about that a number of years ago.

There was a consensus at that time about genetic testing which has crumbled away in the intervening years because first more tests have come up and the genetics' star is shining -- the simplistic genetics' star is shining. So it might very well be that we have to revisit that.

MS. KRAMER: I have great concern about that because of some of the advertisements, the strong advertising campaigns that are under way by certain institutions urging women, particularly, to get tested for breast cancer, for BRZ-1-2, and these women are

going in there assuming that there's something that can be done. I mean, it's a problem. I think we need to consider it.

CHAIR CHILDRESS: This may well be, and maybe we can ask staff to include -- other comments that have come out about other things. I would note that the list, actually, of immediate concerns, as well as long-term, that list focuses more on the research side of our dual mission than on the genetic side.

The use and management of genetic information is one of our two major concerns. This would seem to me to fit quite appropriately under that, and perhaps would add a bit more of the genetics side to the list of topics to look at over time.

DR. CASSELL: Well, now that we have more staff, and really a highly professional staff, that seems to me to be something that could be reproduced as a document, as a contract document, a discussion of genetic testing in its place and so forth, which then, after we have reviewed it, goes out under the NBAC seal.

NBAC pointing out the problems of genetic testing, where we do not have to raise it as something

to occupy two or three meetings of the Commission. In other words, it's something we ask to be done because we recognize its importance, yet we don't put it on our meeting agenda to occupy us to do it.

CHAIR CHILDRESS: Or if we look at it, we'd decide whether it's something we should put on our agenda to look at.

DR. CASSELL: Yes.

MR. MESLIN: I would only suggest that, procedurally, my sense of how we might want to think of going forward, is once we've produced the list, if you will, the grocery list or wish list of the topics that we think would be appropriate for NBAC to consider, be it within our current mandate or in an infinite mandate, we would then try and prioritize those items in a systematic way.

Then following that, you would hopefully be able to rely on each other and staff to offer the best method for proceeding, whether they be a series of contracted papers or working groups that will provide the necessary data for the Commission to start deliberating.

There would be nothing that would prevent a

paper on this subject, but there would be nothing to prevent a Commission paper on any of the subjects that are currently in that planning bucket.

You might also wish to consider, and this will come up probably in the memo that we prepare for you, that there has been an awful lot of work done by the National Human Genome Research Institute and the Department of Energy. A major task force has issued its report. There is an awful lot that has been going on.

When Francis Collins, the director of the Genome Institute spoke at the first NBAC meeting, I think he provided an overview of many of those subjects. Staff would probably be delighted to go over that initial listing and flesh out in more detail what those potential topics would be.

CHAIR CHILDRESS: Are there other points that you would like to make as we move closer to adjournment.

(No response)

CONCLUSIONS

CHAIR CHILDRESS: It says Conclusions. I don't really think I need to offer any. We have talked about what we need to do to prepare the report on the decisionally impaired subjects, or whatever title we come up with.

I guess that might actually be an appropriate thing to close with, is any other thoughts about what direction we might go in terms of categories to use or a category to use toward the report, since questions emerged about research subjects with questionable capacity, as well as questions that emerged about every other category.

You may not have any thoughts today, but this is something we obviously need to think about, since it

does raise issues for a variety of issues. These terms apply various things for different individuals, and we do need to be aware of how they might be perceived.

DR. CASSELL: I thought that that was a safe -- impairment of decision making capacity was a -- but it isn't, is it?

CHAIR CHILDRESS: I think questions have been raised.

PROFESSOR BACKLAR: I think it's interesting to look at Paul Applebaum's -- and we might want to take clues from that. Not to copy it, necessarily, just the nature of disorders that affect decision making ability. I'm not certain exactly how one affects the disorders that affect decision making ability -- some way of visualizing this.

DR. CASSELL: All I -- decisionally challenged.

DR. SCOTT-JONES: Jim.

CHAIR CHILDRESS: Yes.

DR. SCOTT-JONES: What was the deadline we gave ourselves for responding to the draft of this paper?

CHAIR CHILDRESS: One week.

DR. MORENO: One week.

CHAIR CHILDRESS: We said one week. But would you like to try to sneak in 10 days? One week. All right.

DR. MORENO: One week.

CHAIR CHILDRESS: One week.

One last thing. Eric reminds me that there has been some discussion about getting a paper that looks at the various kinds of assumptions in trying to determine incompetence, incapacity, or lack of capacity, the kinds of measurements that Paul Applebaum and others have developed. There's been some discussion that Alex, Trish, Eric and I have been involved with about a possible paper in that direction.

Any thoughts about that? This is one other contract paper that could be useful to us, and perhaps could be, if not available in -- couldn't be available in full form by the time we need, but we might be able to get a possible contractor to talk with us about the kinds of issues that are involved in measurement in some type of capacity. Is that an area where we'd like to have some kind of report on this in February?

DR. BRITO: That would be useful. I wouldn't

be surprised if what we come up with is -- well, we know that there's a lack of standardization, and it may actually open up another area where -- go ahead. Were you going to say something?

DR. CASSELL: It's a can of worms.

DR. BRITO: It's a can of worms. But it would be useful just to find that out.

CHAIR CHILDRESS: I was intrigued by the Maryland approach, which was at least through the -- people to investigators to indicate how they're going about determining this, and that's obviously one kind of procedural way to go. But it may be useful for us to look at some of the issues involved, so we will try to do that.

Any last points that people would like to make?

(No response)

CHAIR CHILDRESS: Well, I thank you for your forbearance. I thank the others who were here for their contributions. We really appreciate the work of staff. We thank you very much for all that you've done to make this period of two days very successful. Thank you. Thanks, everyone.

(Whereupon, at 11:56 a.m., the meeting was concluded.)

C E R T I F I C A T E

This is to certify that the foregoing proceedings of a meeting of the National Bioethics Advisory Commission, Human Subjects Subcommittee, held on January 8, 1998, were transcribed as herein appears, and this is the original of transcript

thereof.

WILLIAM J. MOFFITT

Official Court Reporter